Exercise During Active Surveillance for Prostate Cancer: The ERASE Trial

by

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ABSTRACT

Background: Prostate cancer treatments often lead to side effects including sexual and urinary dysfunction as well as fatigue and poor quality of life. As a means of avoiding these side effects, active surveillance has been introduced as a strategy to manage men with low- to moderate-grade prostate cancer. In active surveillance, treatments are delayed until the prostate cancer becomes clinically significant. Despite the advantages of active surveillance, many men still require radical treatments eventually, have a higher risk of metastasis, and experience psychosocial distress. Interventions that slow the progression of the disease, manage anxiety and fear of cancer progression, and better prepare men for impending radical treatments would be highly beneficial. Exercise delays the progression of prostate tumours in animal models through alterations in immune function; however, these findings have not been confirmed in men with prostate cancer. Moreover, exercise improves quality of life in prostate cancer patients during and after radical treatments but no study to date has focused on men with prostate cancer on active surveillance or examined fear of cancer progression. Finally, exercise may serve as a prehabilitation strategy in the oncology setting but no study to date has examined fitness outcomes that may be associated with posttreatment recovery in men with prostate cancer on active surveillance.

Purpose: The primary purpose of this dissertation was to examine the effects of exercise on cardiopulmonary fitness as a surrogate marker of prostate cancer outcomes, patient-reported outcomes, and posttreatment complications in prostate cancer patients on active surveillance. Secondary aims were to examine the impacts of the intervention on cancer-related biomarkers, physical fitness, and psychosocial outcomes.

Methods: This study was a phase II randomized controlled trial in 52 men with localized prostate cancer undergoing active surveillance. Participants were randomly allocated to either

high-intensity aerobic interval exercise (HIIT, n=26) or usual care (UC, n=26). The primary outcome was cardiopulmonary fitness. Secondary outcomes included cancer-related biomarkers, patient-reported psychosocial outcomes and cancer-related symptoms, and physical and functional fitness.

Results: Participants were recruited from July 2018 to February 2020. Overall, 361 men with PCa undergoing AS were screened, 176 (51%) were eligible, and 52 (30%) were randomized with 26 participants per group. There were two dropouts from the HIIT group (unwillingness; medical issue) and one from the UC group (no contact). A total of 46 participants (88%) completed the postintervention VO_{2peak} assessment and 49 (94%) completed the postintervention functional fitness assessment and blood draw. The primary outcome of VO_{2peak} significantly improved in the HIIT group compared to the UC group (adjusted between-group mean difference, 1.6 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% confidence interval [CI], 0.3 to 2.9; p=0.014). HIIT also exerted a significant reduction in PSA levels (adjusted between-group mean difference, -1.1 ug/L; 95% CI, -2.1 to 0.0; p=0.043) and PSA velocity (adjusted between-group mean difference, -1.3 ug·L-1·year-1; 95% CI, -2.5 to -0.1; p=0.040). There were significant improvements in cardiometabolic and inflammatory markers including total cholesterol (p=0.011), non-HDL-C (p=0.006), IL-1β (p=0.006), IL-4 (p=0.017), and IL-12p70 (p=0.009) and psychological outcomes including prostate cancer-specific anxiety (p=0.024) and fear of cancer progression (p=0.013), hormonal symptoms (p=0.005), perceived stress (p=0.037), fatigue (p=0.029), and self-esteem (p=0.007).

Conclusions: HIIT improved cardiopulmonary fitness, biochemical progression of prostate cancer, systemic lipid and inflammatory markers, and prostate cancer-specific anxiety. These findings suggest clinical benefits of HIIT in active surveillance setting such as delaying radical

treatment through suppressing prostate cancer progression and addressing fear of cancer progression. Also, the improvement of cardiopulmonary fitness may prepare these men for possible radical treatment. Larger phase II/III trials are warranted to confirm the longer-term clinical benefits of exercise in the active surveillance setting.

PREFACE

This dissertation is an original work by Dong-Woo Kang. The doctoral project entitled "Exercise During Active Surveillance for Prostate Cancer: The ERASE Trial" received research ethics approval from the Health Research Ethics Board of Alberta-Cancer Committee (HREBA.CC-17-0248) on January 9, 2018 and from the Northern Alberta Clinical Trials and Research Centre (NACTRC OA39314) on March 19, 2018.

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LIST OF KEY ABBREVIATIONS

AS: active surveillance

HIIT: high-intensity interval training

NK: natural killer

PCa: prostate cancer

PSA: prostate-specific antigen

QOL: quality of life

UC: usual care

VO_{2peak}: peak volume of oxygen consumption

CHAPTER 1 – INTRODUCTION

1.1 Prostate Cancer

Prostate cancer (PCa) is the most common cancer in Canadian men, accounting for 20.3% of all estimated new cancer cases (approximately 22,900 cases) in 2019 and the lifetime probability of developing PCa is 11.3% [1]. Although the incidence rate of PCa has been increasing over the past decades due to the introduction of prostate-specific antigen (PSA) a as a means of PCa early detection, the 10-year overall survival rate for PCa is as high of 90-95% [1, 2]. Patients who have an early-staged PCa do not often show noticeable signs or symptoms, but when the prostate tumour is in advanced stages, patients may report several symptoms including frequent urination, difficulty in starting or stopping urinating, blood in urine, and sexual dysfunction [3]. Most PCa patients often undergo conventional treatments including radical prostatectomy, external beam radiation therapy, brachytherapy, and androgen deprivation therapy [4]. However, these treatments can cause side effects such as physical, sexual, and urinary dysfunctions as well as fatigue and poor quality of life [5].

In recent years, a clinical practice, “active surveillance (AS)”, has been introduced in low- or intermediate-risk PCa patients [6]. Under AS, PCa patients are not receiving any immediate treatment but closely monitored using repeated prostate biopsies, digital rectal exams, and/or serum PSA concentrations to determine whether there are any signs of tumour progression [7]. AS allows early-stage PCa patients to avoid radical treatments/side effects and reduce potential risks of tumour spreading during surgery, as well as to maintain quality of life [8] without compromising survival benefits of radical treatments [9]. Due to these advantages, the number of PCa patients who choose AS as the primary strategy for their PCa management has been substantially increasing from approximately 15% in 2010 to 45% in 2015 [10]. Moreover, AS offers substantial medical cost saving over radical treatments up to approximately

$8,000 per patient [11-13]. For the detailed review of the conventional treatment options and AS for early-stage PCa, please see **Appendix A**.

However, despite the advantages of PCa, many PCa patients will still eventually progress to traditional radical treatments. Approximately 30% of men on AS will have radical treatment within three years and 55% within 10 years [9]. Moreover, the risk of metastasis or disease progression is higher in PCa patients who were on AS compared to those who had undergone radical treatments [9]. Furthermore, it has been reported that PCa patients on AS experience psychological distress such as anxiety and fear of cancer progression, which is an understandable and legitimate concern based on the fact that they have an existing yet untreated tumour possessing a possibility of progressing [14]. Such psychological distress (i.e., fear and anxiety of possible cancer progression) is significantly associated with poor quality of life [15] and may even prompt these men and their doctors to opt for radical treatments as a way of managing anxiety [16]. Unfortunately, most clinical practices do not provide PCa patients on AS with any formal behavioural guidance or intervention that may help slow tumour progression, improve quality of life, and prepare for impending radical treatments. Interventions during AS to address this unmet clinical need would be highly beneficial.

1.2 Lifestyle Interventions During Active Surveillance

One promising line of inquiry is examining the potential role of lifestyle interventions in men with PCa on AS. For example, one study investigated the effects of a year-long intensive lifestyle program (i.e., diet, moderate-intensity aerobic exercise, stress management, and group support session) on PCa progression and health-related quality of life in PCa patients on AS [17]. A few other clinical trials in PCa on AS also employed lifestyle interventions such as a combined

whole-grain diet and vigorous exercise program [18] or a weight loss program using diet and physical activity [19]. In brief, these small number of lifestyle interventions have shown the beneficial effects on quality of life and psychological distress management [20, 21] as well as clinical outcomes such as a reduction in PSA levels [21-23], LNCaP PCa cell growth [22], and clinical events [24]. For a detailed summary of the lifestyle intervention trials in PCa patients on AS, please see **Appendix B**. As might be expected, however, these early preliminary studies have substantial limitations including few randomized controlled trials, small sample sizes, unsupervised exercise interventions, and the testing of packaged lifestyle interventions that do not allow the disentangling of the key active components of the intervention.

1.3 Exercise in Prostate Cancer Patients

Exercise is a key lifestyle intervention that may have independent benefits in PCa patients on AS. A body of evidence from meta-analyses [25-27] have demonstrated the positive impacts of exercise in PCa patients on health-related fitness [28-31], physical functioning [29-35], body composition [29-32, 35], fatigue [30-32, 34], and quality of life [30-32, 34, 36]. Moreover, observational studies have reported an association between an increased level of physical activity and a reduced PCa risk [37-42] and progression/mortality [43-47]. For a detailed summary of the effects of exercise in PCa patients and the relationship between physical activity and PCa, please see **Appendix C**. Furthermore, exercise has been shown to improve physical fitness, decrease hospital stay/readmissions, and facilitate recovery from surgical treatment as a means of "prehabilitation" in other cancer patient groups [48, 49]. Finally, a number of preclinical experiments have examined the biological links between exercise and the tumour itself [50], where exercise inhibits prostate tumour growth through various bio-

physiological mechanisms [51, 52]. However, most exercise clinical trials in PCa patients have focused on the effects of resistance or combined aerobic and resistance exercise during PCa hormonal therapy (i.e., androgen deprivation therapy) and a few studies conducted in post-surgical settings [25, 26]. To date, only one clinical trial showed the feasibility and acceptability and preliminary efficacy of exercise during AS [53], and one ongoing trial is examining the effects of a 3-year long aerobic and resistance exercise program on the need for invasive treatment [54].

In terms of maximizing these potential benefits of exercise in AS patients, a body of evidence supports that higher-intensity exercise programs often produce greater health benefits compared to moderate-intensity continuous training [55, 56]. High-intensity interval training (HIIT) aerobic exercise is a type of high-intensity exercise, alternating short periods of intense exercise and active recovery. HIIT has been shown to induce better clinical outcomes such as cardiopulmonary fitness and cardiovascular disease (CVD) risk factors in patients with heart disease, compared to traditional moderate-intensity exercise [56-59]. Moreover, HIIT was not only feasible and safe in several types of cancer patients but also beneficial in improving physical fitness and mental health [60-63]. Finally, given that higher-intensity exercise may be required to induce a sufficient increase in natural killer (NK) cell infiltration to kill tumour cells (up to 60% in animal models), it is plausible that HIIT may be a powerful intervention that can boost cancer surveillance and therefore tumour suppression in AS patients [64, 65].

1.4 Rationale and Objectives

Taken together, current evidence supports that PCa patients undergoing AS are in a "window of opportunity", where they would benefit from exercise that can suppress tumour

progression and reduce physical and mental side effects from cancer and its treatments. Furthermore, newly diagnosed cancer patients can benefit from optimizing their health before starting acute treatments [49], which provides opportunities to use a prehabilitation exercise intervention in AS patients to facilitate recovery from potential radical treatment [48, 49, 66].

Exercise has been shown to delay the progression of prostate tumours in animal models [51]; however, these findings have not been confirmed in men with PCa. Moreover, exercise has been shown to improve physical fitness, physical functioning, body composition, fatigue, and quality of life during and after radical PCa treatments [67], but no study has focused on the AS setting or examined "fear of cancer progression" - the psychological construct most likely to result in unnecessary medical intervention. Furthermore, exercise may help prepare PCa patients for radical treatments (i.e., prehabilitation) [49] but current studies are only preliminary and none have focused on PCa patients on AS.

Therefore, the overarching objective of this dissertation was to investigate the effects of exercise on cardiopulmonary and functional fitness, biochemical progression of PCa, cancer-related biomarkers, and patient-reported outcomes in PCa patients on AS. I hypothesized that, compared to UC, a 12-week aerobic HIIT program would improve cardiopulmonary fitness, functional fitness, biochemical progression of PCa, cancer-related biomarkers, and patient-reported outcomes in PCa patients undergoing AS.

1.5 Overview of the Dissertation

The dissertation is comprised of four papers and discussion. **Chapter 2** (paper 1) described the detailed rationale of the Exercise During Active Surveillance for Prostate Cancer (ERASE) Trial, the proposed theoretical model, and the protocol of the study. **Chapter 3** (paper

2) reports the primary findings from the ERASE Trial focusing on the effects of high-intensity interval training on cardiopulmonary fitness and biochemical progression of PCa. **Chapter 4** (paper 3) reports the effects of HIIT on cardiometabolic and inflammatory biomarkers from the ERASE Trial. **Chapter 5** (paper 4) reports the effects of HIIT on patient-reported outcomes including fear of cancer progression and anxiety from the ERASE Trial. Lastly, **Chapter 6** integrates the above four chapters (Chapter 2 to 5) and discusses the overall findings of the ERASE Trial, strengths and limitations, future research directions, practical implications, and final conclusions.

1.6 References

1. Canadian Cancer Society, *Canadian Cancer Statistics 2019*. 2019.
2. Neal DE, Metcalfe C, Donovan JL, Lane JA, Davis M, Young GJ, et al., Ten-year Mortality, Disease Progression, and Treatment-related Side Effects in Men with Localised Prostate Cancer from the ProtecT Randomised Controlled Trial According to Treatment Received. *European Urology*, 2020. **77**(3): p. 320-30.
3. Talcott JA, Rieker P, Clark JA, Propert KJ, Weeks JC, Beard CJ, et al., Patient-reported symptoms after primary therapy for early prostate cancer: results of a prospective cohort study. *J Clin Oncol*, 1998. **16**(1): p. 275-83.
4. National Comprehensive Cancer Network (NCCN), *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer*. 2019.
5. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al., Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1425-37.
6. Parker C, Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol*, 2004. **5**(2): p. 101-6.
7. Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR, et al., Active surveillance for prostate cancer: a systematic review of the literature. *Eur Urol*, 2012. **62**(6): p. 976-83.
8. Cooperberg MR, Carroll PR, and Klotz L, Active surveillance for prostate cancer: progress and promise. *J Clin Oncol*, 2011. **29**(27): p. 3669-76.

9. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al., 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1415-24.

10. Mahal BA, Butler S, Franco I, Spratt DE, Rebbeck TR, D'Amico AV, et al., Use of Active Surveillance or Watchful Waiting for Low-Risk Prostate Cancer and Management Trends Across Risk Groups in the United States, 2010-2015. *JAMA*, 2019. **321**(7): p. 704-6.

11. Dall'Era MA, The economics of active surveillance for prostate cancer. *Curr Opin Urol*, 2013. **23**(3): p. 278-82.

12. Keegan KA, Dall'Era MA, Durbin-Johnson B, and Evans CP, Active surveillance for prostate cancer compared with immediate treatment: an economic analysis. *Cancer*, 2012. **118**(14): p. 3512-8.

13. Dragomir A, Cury FL, and Aprikian AG, Active surveillance for low-risk prostate cancer compared with immediate treatment: a Canadian cost comparison. *CMAJ Open*, 2014. **2**(2): p. E60-8.

14. Wallace M, Uncertainty and quality of life of older men who undergo watchful waiting for prostate cancer. *Oncology nursing forum*, 2002. **30**(2): p. 303-9.

15. Parker PA, Davis JW, Latini DM, Baum G, Wang X, Ward JF, et al., Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with favourable-risk prostate cancer undergoing active surveillance. *BJU Int*, 2016. **117**(3): p. 469-77.

16. Latini DM, Hart SL, Knight SJ, Cowan JE, Ross PL, Duchane J, et al., The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. *J Urol*, 2007. **178**(3 Pt 1): p. 826-31; discussion 31-2.

17. Ornish DM, Lee KL, Fair WR, Pettengill EB, and Carroll PR, Dietary trial in prostate cancer: Early experience and implications for clinical trial design. *Urology*, 2001. **57**(4 Suppl 1): p. 200-1.

18. Eriksen AK, Hansen RD, Borre M, Larsen RG, Jensen JM, Overgaard K, et al., A lifestyle intervention among elderly men on active surveillance for non-aggressive prostate cancer: a randomised feasibility study with whole-grain rye and exercise. *Trials*, 2017. **18**(1): p. 20.

19. Demark-Wahnefried W, Nix JW, Hunter GR, Rais-Bahrami S, Desmond RA, Chacko B, et al., Feasibility outcomes of a presurgical randomized controlled trial exploring the impact of caloric restriction and increased physical activity versus a wait-list control on tumor characteristics and circulating biomarkers in men electing prostatectomy for prostate cancer. *BMC Cancer*, 2016. **16**(1): p. 61.

20. Daubenmier JJ, Weidner G, Marlin R, Crutchfield L, Dunn-Emke S, Chi C, et al., Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance. *Urology*, 2006. **67**(1): p. 125-30.

21. Ornish D, Lin J, Daubenmier J, Weidner G, Epel E, Kemp C, et al., Increased telomerase activity and comprehensive lifestyle changes: a pilot study. *Lancet Oncol*, 2008. **9**(11): p. 1048-57.

22. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al., Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*, 2005. **174**(3): p. 1065-9; discussion 9-70.

23. Ornish D, Lin J, Chan JM, Epel E, Kemp C, Weidner G, et al., Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *Lancet Oncol*, 2013. **14**(11): p. 1112-20.

24. Frattaroli J, Weidner G, Dnistrian AM, Kemp C, Daubenmier JJ, Marlin RO, et al., Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology*, 2008. **72**(6): p. 1319-23.

25. Bourke L, Smith D, Steed L, Hooper R, Carter A, Catto J, et al., Exercise for Men with Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol*, 2016. **69**(4): p. 693-703.

26. Keilani M, Hasenoehrl T, Baumann L, Ristl R, Schwarz M, Marhold M, et al., Effects of resistance exercise in prostate cancer patients: a meta-analysis. *Support Care Cancer*, 2017. **25**(9): p. 2953-68.

27. Vashistha V, Singh B, Kaur S, Prokop LJ, and Kaushik D, The Effects of Exercise on Fatigue, Quality of Life, and Psychological Function for Men with Prostate Cancer: Systematic Review and Meta-analyses. *Eur Urol Focus*, 2016. **2**(3): p. 284-95.

28. Jones LW, Hornsby WE, Freedland SJ, Lane A, West MJ, Moul JW, et al., Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized prostate cancer. *Eur Urol*, 2014. **65**(5): p. 852-5.

29. Cormie P, Newton RU, Spry N, Joseph D, Taaffe DR, and Galvao DA, Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. *Prostate Cancer Prostatic Dis*, 2013. **16**(4): p. 328-35.

30. Cormie P, Galvão DA, Spry N, Joseph D, Chee R, Taaffe DR, et al., Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU international*, 2015. **115**(2): p. 256-66.

31. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al., Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*, 2009. **27**(3): p. 344-51.

32. Galvao DA, Taaffe DR, Spry N, Joseph D, and Newton RU, Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*, 2010. **28**(2): p. 340-7.

33. Park SW, Kim TN, Nam JK, Ha HK, Shin DG, Lee W, et al., Recovery of overall exercise ability, quality of life, and continence after 12-week combined exercise intervention in elderly patients who underwent radical prostatectomy: a randomized controlled study. *Urology*, 2012. **80**(2): p. 299-305.

34. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, et al., Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol*, 2003. **21**(9): p. 1653-9.

35. Uth J, Hornstrup T, Schmidt JF, Christensen JF, Frandsen C, Christensen KB, et al., Football training improves lean body mass in men with prostate cancer undergoing androgen deprivation therapy. *Scand J Med Sci Sports*, 2014. **24 Suppl 1**(S1): p. 105-12.

36. Farris MS, Kopciuk KA, Courneya KS, McGregor SE, Wang Q, and Friedenreich CM, Identification and prediction of health-related quality of life trajectories after a prostate cancer diagnosis. *Int J Cancer*, 2017. **140**(7): p. 1517-27.

37. Pierotti B, Altieri A, Talamini R, Montella M, Tavani A, Negri E, et al., Lifetime physical activity and prostate cancer risk. *Int J Cancer*, 2005. **114**(4): p. 639-42.

38. Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, and Elliott FG, Case-control study of lifetime total physical activity and prostate cancer risk. *Am J Epidemiol*, 2004. **159**(8): p. 740-9.

39. Giovannucci EL, Liu Y, Leitzmann MF, Stampfer MJ, and Willett WC, A prospective study of physical activity and incident and fatal prostate cancer. *Arch Intern Med*, 2005. **165**(9): p. 1005-10.

40. Johnsen NF, Tjonneland A, Thomsen BL, Christensen J, Loft S, Friedenreich C, et al., Physical activity and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Int J Cancer*, 2009. **125**(4): p. 902-8.

41. Liu Y, Hu F, Li D, Wang F, Zhu L, Chen W, et al., Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *European urology*, 2011. **60**(5): p. 1029-44.

42. Orsini N, Bellocco R, Bottai M, Pagano M, Andersson SO, Johansson JE, et al., A prospective study of lifetime physical activity and prostate cancer incidence and mortality. *Br J Cancer*, 2009. **101**(11): p. 1932-8.

43. Giovannucci EL, Liu Y, Leitzmann MF, Stampfer MJ, and Willett WC, A prospective study of physical activity and incident and fatal prostate cancer. *Archives of internal medicine*, 2005. **165**(9): p. 1005-10.

44. Kenfield SA, Stampfer MJ, Giovannucci E, and Chan JM, Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol*, 2011. **29**(6): p. 726-32.

45. Friedenreich CM, Wang Q, Neilson HK, Kopciuk KA, McGregor SE, and Courneya KS, Physical Activity and Survival After Prostate Cancer. *Eur Urol*, 2016. **70**(4): p. 576-85.

46. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, and Chan JM, Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. *Cancer Res*, 2011. **71**(11): p. 3889-95.

47. Bonn SE, Sjolander A, Lagerros YT, Wiklund F, Stattin P, Holmberg E, et al., Physical activity and survival among men diagnosed with prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 2015. **24**(1): p. 57-64.

48. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al., Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surg Endosc*, 2013. **27**(4): p. 1072-82.

49. Silver JK and Baima J, Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *American Journal of Physical Medicine & Rehabilitation*, 2013. **92**(8): p. 715-27.

50. Ashcraft KA, Peace RM, Betof AS, Dewhirst MW, and Jones LW, Efficacy and Mechanisms of Aerobic Exercise on Cancer Initiation, Progression, and Metastasis: A

Critical Systematic Review of In Vivo Preclinical Data. *Cancer Res*, 2016. **76**(14): p. 4032-50.

51. Jones LW, Antonelli J, Masko EM, Broadwater G, Lascola CD, Fels D, et al., Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. *J Appl Physiol (1985)*, 2012. **113**(2): p. 263-72.

52. Hayes BD, Brady L, Pollak M, and Finn SP, Exercise and Prostate Cancer: Evidence and Proposed Mechanisms for Disease Modification. *Cancer Epidemiol Biomarkers Prev*, 2016. **25**(9): p. 1281-8.

53. Bourke L, Stevenson R, Turner R, Hooper R, Sasieni P, Greasley R, et al., Exercise training as a novel primary treatment for localised prostate cancer: a multi-site randomised controlled phase II study. *Sci Rep*, 2018. **8**(1): p. 8374.

54. Galvao DA, Hayne D, Frydenberg M, Chambers SK, Taaffe DR, Spry N, et al., Can exercise delay transition to active therapy in men with low-grade prostate cancer? A multicentre randomised controlled trial. *BMJ Open*, 2018. **8**(4): p. e022331.

55. Helgerud J, Hoydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, et al., Aerobic high-intensity intervals improve VO2max more than moderate training. *Medicine and Science in Sports and Exercise*, 2007. **39**(4): p. 665-71.

56. Gibala MJ, Little JP, Macdonald MJ, and Hawley JA, Physiological adaptations to low-volume, high-intensity interval training in health and disease. *J Physiol*, 2012. **590**(5): p. 1077-84.

57. Poole DC and Gaesser GA, Response of ventilatory and lactate thresholds to continuous and interval training. *J Appl Physiol (1985)*, 1985. **58**(4): p. 1115-21.

58. Warburton DE, McKenzie DC, Haykowsky MJ, Taylor A, Shoemaker P, Ignaszewski AP, et al., Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *Am J Cardiol*, 2005. **95**(9): p. 1080-4.

59. Moholdt TT, Amundsen BH, Rustad LA, Wahba A, Lovo KT, Gullikstad LR, et al., Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *Am Heart J*, 2009. **158**(6): p. 1031-7.

60. Licker M, Karenovics W, Diaper J, Fresard I, Triponez F, Ellenberger C, et al., Short-Term Preoperative High-Intensity Interval Training in Patients Awaiting Lung Cancer Surgery: A Randomized Controlled Trial. *J Thorac Oncol*, 2017. **12**(2): p. 323-33.

61. Schmitt J, Lindner N, Reuss-Borst M, Holmberg HC, and Sperlich B, A 3-week multimodal intervention involving high-intensity interval training in female cancer survivors: a randomized controlled trial. *Physiol Rep*, 2016. **4**(3).

62. Toohey K, Pumpa KL, Arnolda L, Cooke J, Yip D, Craft PS, et al., A pilot study examining the effects of low-volume high-intensity interval training and continuous low to moderate intensity training on quality of life, functional capacity and cardiovascular risk factors in cancer survivors. *PeerJ*, 2016. **4**: p. e2613.

63. Devin JL, Sax AT, Hughes GI, Jenkins DG, Aitken JF, Chambers SK, et al., The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: a randomised controlled trial. *J Cancer Surviv*, 2016. **10**(3): p. 467-79.

64. Sasso JP, Eves ND, Christensen JF, Koelwyn GJ, Scott J, and Jones LW, A framework for prescription in exercise-oncology research. *J Cachexia Sarcopenia Muscle*, 2015. **6**(2): p. 115-24.

65. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al., Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. *Cell Metab*, 2016. **23**(3): p. 554-62.

66. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al., Intensive lifestyle changes may affect the progression of prostate cancer. *The Journal of urology*, 2005. **174**(3): p. 1065-70.

67. Bourke L, Smith D, Steed L, Hooper R, Carter A, Catto J, et al., Exercise for men with prostate cancer: a systematic review and meta-analysis. *European urology*, 2016. **69**(4): p. 693-703.

CHAPTER 2 – PAPER 1 (Rationale and Protocol)

Exercise duRing Active Surveillance for prostatE cancer: the ERASE trial

- A study protocol of a phase II randomized controlled trial

A version of this chapter has been published.

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2.1 Abstract

Background: Active surveillance (AS) is the preferred primary treatment strategy for men with low-risk clinically localised prostate cancer (PCa); however, the majority of these men still receive radical treatment within 10 years due to disease progression and/or fear of cancer progression. Interventions designed to suppress tumour growth, mitigate fear of cancer progression and precondition men for impending radical treatments are an unmet clinical need. Exercise has been shown to delay the progression of prostate tumours in animal models, improve physical and functional health and manage psychological outcomes in cancer patients; however, these outcomes have not been demonstrated in PCa patients undergoing AS.

Methods: This phase II randomised controlled trial will randomise 66 men undergoing AS to either an exercise group or a usual care group. The exercise group will perform a 12-week, supervised, high-intensity interval training programme, consisting of 3 sessions/week for 28–40 min/session. The primary outcome will be cardiorespiratory fitness. Secondary outcomes will include immunosurveillance and cancer-related biomarkers, psychosocial outcomes including fear of cancer progression and quality of life and physical function. Exploratory outcomes will include clinical indicators of disease progression. The trial has 80% power to detect a significant between-group difference in VO_{2peak} of 3.5 mL/kg/min with a two-tailed alpha level <0.05 and a 10% dropout rate.

Discussion: This study will be the first randomized controlled trial to test a high-intensity interval training intervention in men with prostate cancer undergoing active surveillance. Strengths and limitations of this study include: (1) the intervention is fully supervised and designed to maximize improvements in aerobic fitness and biological outcomes; (2) this study will examine important intermediate outcomes including biomarkers relating to cancer

surveillance and tumour growth, and fear of cancer progression; (3) this study is not powered to examine the key clinical outcomes of progression to radical treatment and posttreatment complications; and (4) the intervention is only 12 weeks long and there is a usual care cross-over that will confound longer term comparisons.

2.2 Introduction

Conventionally, prostate cancer (PCa) is treated immediately by radical prostatectomy, radiation therapy and/or hormonal therapy [1]. These treatments improve overall survival; however, they are expensive and cause side-effects such as sexual and urinary dysfunction, fatigue, loss of lean body mass, muscle weakness and reduced quality of life [2-4]. Active surveillance (AS) has emerged as an alternative clinical practice that is offered to men with low-to-favourable intermediate risk of PCa [5]. In AS, men with PCa do not receive any immediate radical treatments but are closely monitored for any signs of tumour progression. The obvious advantage of AS is that it allows early-stage PCa patients to avoid treatment-related side-effects without compromising their PCa-specific and overall survival [3, 6]. Moreover, there is substantial cost saving over radical treatments [7-10].

Unfortunately, many men with PCa on AS eventually experience disease progression and require radical treatments. Approximately 30% of men on AS receive radical treatments within 3 years and about 55% within 10 years [6]. Moreover, even without an objective progression of their disease, many AS patients experience anxiety and fear of cancer progression based on having an untreated tumour with a chance of progression [11, 12]. Fear of cancer progression and uncertainty of illness are associated with a poor quality of life [13], which may prompt these men and their doctors to opt for radical treatments as a way of managing the fear and anxiety [14-17].

Evidence shows that exercise may be beneficial to men with PCa on AS in three potential pathways proposed in our model (**Figure 2-1**). First, exercise that is sufficient to improve cardiorespiratory fitness may be linked to slower PCa progression [18]. Several possible biological mechanisms have been studied in animal [19-21], and human [22], models, including

improved immune activity through aerobic exercise which may play a critical role [23]; however, these findings have not been confirmed in men with PCa. Second, exercise has been shown to improve health-related fitness [24-27], treatment-related side-effects [24, 26], physical functioning [25-30], body composition [25-28], fatigue [26-28, 30], and quality of life [26-28, 30, 31], during and after radical PCa treatments, but few studies to date have focused on the AS setting or examined fear of cancer progression. Last, given the eventuality of receiving radical treatment for many PCa patients on AS [6], exercise may help these men improve overall physical condition/function prior to impending radical treatments (ie, prehabilitation) [32], which may reduce anticipated treatment-related side-effects. However, current studies are only preliminary and few have focused on PCa patients on AS. Therefore, we hypothesised that exercise may be a cost-effective intervention that will provide clinical benefits to men with PCa undergoing AS.

The primary objective of the Exercise duRing Active Surveillance for prostatE cancer (ERASE) Trial is to examine the effects of exercise on cardiorespiratory fitness in PCa patients undergoing AS. The secondary objectives are to examine the effects of exercise on: (1) biological markers linked to immune surveillance and PCa, as well as tumour-related metabolic and proinflammatory biomarkers, (2) patient-reported outcomes including fear of cancer progression, anxiety and quality of life and (3) health-related fitness outcomes including physical function and body composition. The exploratory objectives are to examine the effects of exercise on clinical indicators of cancer progression including progression to radical treatments. In this paper, the detailed study design and protocol of the ERASE trial are described based on the Standard Protocol Items for Randomised Trials (SPIRIT) guideline.

2.3 Methods

Study design

The ERASE trial will be a prospective, single centre, two-armed, phase II randomised controlled trial at the University of Alberta and the Northern Alberta Urology Centre (NAUC) in Edmonton, Alberta, Canada. The proposed study activities and assessments by timepoints based on the SPIRIT guideline are presented in **Table 2-1**, and the proposed study participant flow diagram throughout the study is shown in **Figure 2-2**.

Study population

Men will be eligible if they are: (1) ≥18 years old, (2) diagnosed with very low, low or favourable intermediate grade localised PCa defined by the 2017 National Comprehensive Cancer Network (NCCN) Guidelines for PCa [33], (3) undergoing AS as the primary treatment option with no plans for radical treatment at the time of recruitment, (4) medically cleared to participate in the study as determined by their treating urologist and a certified clinical exercise physiologist using the Physical Activity Readiness Questionnaire [34], (5) able to complete the assessment for the primary outcome of the study (ie, maximal aerobic exercise testing) at baseline, (6) free of uncontrolled medical conditions that could be exacerbated with exercise, (7) not participating in any structured high-intensity exercise defined as 0 min of vigorous intensity exercise during a typical week in the past month measured by the modified Godin Leisure-Time Exercise Questionnaire (GLTEQ) [35], and (8) willing to perform all required study assessments and interventions and be randomised to either a 12-week supervised exercise training programme at the University of Alberta or continue with their usual activity for 12 weeks.

Recruitment

Recruitment will be conducted through the NAUC at the Kaye Edmonton Clinic, Edmonton, Canada. Patients will be screened for eligibility through the NAUC medical record and eligible patients will be briefly informed about the study by their physicians during their checkup visits. All interested patients will receive a detailed explanation of the study from the study coordinators and be further screened for current physical activity readiness and participation level for eligibility. Those patients who are eligible and agree to participate will be asked to provide written informed consent for study participation and blood banking.

Randomisation and blinding

Participants will be randomly assigned to either the exercise group or the usual care group in a 1:1 ratio on completion of baseline assessment. The allocation sequence will be produced by computer-generated block randomisation numbers and concealed from study staff involved in recruitment and baseline assessment. Due to the nature of the exercise intervention, it is not possible to blind participants or interventionists to group allocation. Outcome assessors will not always be blinded to group allocation for the physical fitness and body composition outcomes due to logistical issues, but they will be trained in standardised testing procedures. Outcome assessors for other secondary and exploratory outcomes will be blinded.

Interventions

Exercise group

Patients randomised to the exercise group will be asked to complete a 12-week, supervised high-intensity interval training (HIIT) programme (**Table 2-2**; **Figure 2-3**). The exercise will consist of alternating vigorous and low-intensity intervals performed on a treadmill. Exercise frequency will be 3 times per week and the duration of each session will progress from

28 to 40 min. The intensity of the exercise will be modified by changing the treadmill speed and/or grade prescribed at specific workloads corresponding to 85%–95% of peak oxygen consumption (VO_{2peak}) measured at baseline. The exercise programme consists of: (1) 'warm-up' for 5 min at a workload corresponding to 60% of VO_{2peak}, (2) 'high-intensity' phase for 2 min at a gradually increasing workload corresponding to 85%–95% of VO_{2peak} (ie, 85% in the 1st–4th week, 90% in the 5th–8th week and 95% in the 9th–12th week), (3) 'recovery' phase for 2 min at a workload corresponding to 40% of VO_{2peak}, (4) repeated sets of 'high-intensity' and 'recovery' phases (ie, increasing from 5 to 8 sets in the 1st–4th week for initial training adaptation and 8 sets in the 5th–12th week), and (5) 'cool-down' for 5 min at a workload corresponding to 30% of VO_{2peak}). Stretching for lower body muscles (eg, quadriceps, hamstrings and calves) will be followed after each exercise session for 5 min. For the purpose of monitoring exercise intensity and safety, heart rates (HRs) will continuously be monitored throughout each session using a HR monitor (Polar T31; Woodbudy, NY, USA). Over the 12-week intervention period, exercise adherence to the prescribed exercise programme will be monitored and recorded based on attendance at the scheduled exercise sessions, and completion of the prescribed intensity, duration and number of intervals during each exercise session. Strategies to maximise adherence will include appointment-based sessions, flexible scheduling, individualised exercise programme, supervision by certified clinical exercise physiologists, free parking and use of the Behavioural Medicine Fitness Centre which is available only to cancer patients participating in the clinical exercise trials. Any missed sessions will trigger a telephone call with a rescheduling of the exercise session as soon as possible.

Usual care group

Currently, the standard AS care at our site does not include any formal exercise programme or advice. Consequently, participants in the usual care group will be asked not to change their exercise levels from baseline during the 12-week study period. After the postintervention assessments at 12 weeks, patients in the usual care group will be offered a 4-week HIIT programme at our facility and/or referred to a 12-week community-based program [36].

Outcome measurements

All study outcomes will be measured at baseline and postintervention at 12 weeks. Also, questionnaires for patient-reported outcomes, prostate-specific antigen (PSA) for disease progression and medical records for clinical events will be obtained at 6-month and 1-year follow-ups. Study outcome assessment timelines are summarised in **Table 2-1** and the validity and reliability of each outcome are described in the online supplementary table (https://bmjopen.bmj.com/content/9/7/e026438).

Primary outcome

The primary outcome of the study will be cardiorespiratory fitness. Cardiorespiratory fitness will be measured as VO_{2peak} by clinical exercise physiologists who are trained for the standardised treadmill testing protocol (modified Bruce protocol) [37]. The test will be conducted on a treadmill (Woodway 4Front; Waukesha, WI, USA) with direct measures of cardiorespiratory variables using a metabolic cart (Parvo Medics TrueOne 2400; Sandy, UT, USA). After a 5-min warm-up, the test will begin at 1.7 mph and 0% grade, and the speed and incline will increase every 3 min until volitional exhaustion or any testing contraindications occur. During the test, oxygen uptake and HR will be recorded continuously, and blood pressure

(BP) using a manual sphygmomanometer, oxygen saturation using a pulse oximeter and rated perceived exertion level using the modified Borg Scale [38] will be measured every 3 min. After the test, a 5-min active recovery will be conducted at 1.7 mph and 0% grade, and HR and BP will be measured at 2 and 5 min during recovery. VO_{2peak} is defined as the highest oxygen uptake value recorded during the test expressed relative to body mass (ie, mL/kg-1·min-1).

Secondary outcomes

Blood-based outcomes will include biomarkers related to immune surveillance (eg, natural killer (NK) cell counts and cytotoxic activity), PCa progression (eg, PSA), inflammatory cytokines (eg, interferon-γ, interleukin (IL)−1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, tumour-necrosis factor (TNF)-α and c-reactive protein (CRP)), metabolism (eg, serum insulin, glucose, HbA1c, insulin-like growth factor (IGF)-1, IGF binding protein-3, adiponectin and leptin), lipid profiles (eg, high- and low-density lipoprotein cholesterol and triglycerides) and sex hormones (eg, testosterone and progesterone). Blood samples will be collected after 12 hours of fasting at the Kaye Edmonton Clinic Laboratory Services and then directly sent to the biochemistry lab in the Li Ka Shing Centre for Health Research Innovation at the University of Alberta. On collection, mononuclear cells on fresh blood will be isolated on a ficoll gradient and characterised using specific monoclonal antibodies and flow cytometry. The plasma will be frozen and stored in a −80°C freezer, monitored and alarmed and only accessible to authorised personnel. For markers that will be assayed on frozen blood, the samples from baseline and postintervention for each subject will be assayed at the same time for more accurate assessment of change using paired assays plated in random order. The immune phenotype identification and biological measures will be performed by trained technicians who are blinded to the treatments

and trained in the standardised protocol. Appropriate standard and reference samples will be included in each assay.

Patient-reported outcomes will include fear of cancer progression using the Fear of Cancer Recurrence Inventory [39], and Cancer Worry Scale [40], health-related quality of life using the European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire-C30 [41], and PCa-specific health-related quality of life and symptoms using the Expanded Prostate Cancer Index Composite-26. General and prostate-specific anxiety will be assessed using the Spielberger State-Trait Anxiety Inventory [42], and the Memorial Anxiety Scale for Prostate Cancer [43], respectively. Depression will be measured using the Center for Epidemiologic Studies Depression Scale [44], fatigue using the Functional Assessment of Cancer Therapy- Fatigue [45], perceived stress using the Perceived Stress Scale [46], self-esteem using the Rosenberg Self-Esteem Scale [47], and motivation to exercise using Theory of Planned Behaviour [48]. Exercise levels will be assessed using the modified GLTEQ [35]. Patient-reported outcomes will be collected using a set of questionnaires which will be sent to patients via mail and patients will be asked to complete within a week from each assessment date. Physical function will be assessed using the Senior's Fitness Test [49], which includes tests for lower body strength (chair stand), upper body strength (arm curl), lower body flexibility (chair sit and reach), upper body flexibility (back scratch), agility (8-foot up and go) and aerobic fitness (6-min walk test). Body composition will include weight, height, and waist and hip circumferences using scales and tape measures. Physical function and body composition assessments will be conducted by clinical exercise physiologists following the standardised protocols [49] [50].

Exploratory outcomes

Exploratory outcomes will include progression to invasive PCa treatment and any clinically relevant events. Clinical events will be reviewed by research staff who are authorised to have access to patient medical records.

Demographic, behavioural and medical variables, and adverse events

Demographic and behavioural information will be obtained using a self-reported questionnaire at baseline. The questionnaire will assess age, ethnicity, education, marital status, income, employment status, smoking and alcohol consumption. Patients' medical information will be abstracted from the NAUC electronic medical record at baseline, including tumour-related information and any complications or comorbidities. Adverse events will be monitored, assessed and recorded during exercise testing and before and after each exercise session throughout the intervention period.

Sample size

A sample size of 60 participants (30 per group) provides 80% power using a two-tailed alpha <0.05 to detect a statistically significant between-group difference of 1-metabolic equivalent task (1-MET; 3.5 mL/kg/min) on our primary outcome of VO_{2peak}, assuming a SD of 5.6 mL/kg/min and adjustment for baseline value and other covariates. It will also be sufficient for detecting differences in our secondary biomarkers and patient-reported outcomes [51]. Considering a potential dropout rate of <10% based on our previous exercise oncology trials [52-55], a total of 66 participants (33 per group) will be randomised. This power will also be sufficient for detecting differences in our secondary biomarkers and patient-reported outcomes if the effects are moderate (ie, a standardised effect size of $d \geq 0.6$ approximately). This power is not sufficient for detecting potentially meaningful differences in any of the exploratory clinical

outcomes. Given that the purpose of this phase II trial is to inform larger phase II and III trials, the patient-reported and clinical outcomes will also be interpreted for potential clinical significance based on the direction and magnitude of numerical differences.

Data collection and management

All data will be collected and stored anonymised in the Behavioural Medicine Laboratory at the University of Alberta in a locked filing cabinet or in a secured, web-based application for electronic data using the Research Electronic Data Capture tools [56]. Data files will only be accessible to study investigators and authorised personnel for data entry and quality control purposes. Data quality will be assured using the double data entry/data comparison and data quality modules [56], by an independent research personnel who will be blinded to the origin of the data.

Statistical analysis

We will conduct descriptive analyses for participant characteristics, intervention adherence and compliance rates, adverse events, and exploratory outcomes of disease progression and clinical events. Analyses of covariance will be performed for the primary and secondary outcomes to compare the between-group differences at postintervention after adjustment for potential covariates. Covariates will be selected a priori and include baseline value and other baseline variables that appear unbalanced between the two groups. If an outcome variable presents a non-normal distribution, log data transformations will be conducted for analyses. All statistical analyses will include all study participants with baseline and follow-up data and will be conducted based on the intention-to-treat principle. Any reasons for missing intervention sessions or study drop-out will be assessed and reported. If missing data is <10%,

we will conduct a complete case analysis. If missing data is ≥10%, we will employ a multiple imputation missing data strategy [57]. Interpretation of the data will be based on the p-value of a two-tailed alpha <0.05, meaningful effect sizes (d≥0.5 for the secondary outcomes) and the general patterns of the findings.

Patient and public involvement

The conception, design, and outcome measures for this study were informed by previous research in PCa patients concerning their priorities for important outcomes and their preferences for exercise intervention. Patients will not be directly involved in the recruitment or conduct of the study. The burden of intervention will be assessed by patients themselves at postintervention through a questionnaire (eg, 'Exercise programme too demanding or difficult'). The results and current progress of the study will be disseminated to the study participants via email and a study webpage (www.erasestudy.com).

2.4 Discussion

AS has become a preferred strategy for the management of early-stage PCa patients; however, many men experience progression and anxiety. Cost-effective interventions that can slow tumour progression, manage fear of cancer progression and prepare PCa patients on AS for impending radical treatments would be highly beneficial. To date, however, no such interventions are offered as standard of care in this clinical setting.

There have been a few lifestyle intervention trials in men with PCa on AS. One randomised controlled trial with 93 PCa patients on AS provided a 1-year lifestyle programme comprising a vegan diet, walking exercise and stress management [58-62]. At the 3-month

interim analyses, the study reported significant improvements in cardiovascular risk factors such as body mass index, BP and lipid profile, as well as several indicators of psychological functioning including mental component summary, intrusive thoughts and avoidance [61]. PSA levels as a cancer progression outcome were not significantly changed but clinically meaningful changes were found [61]. At 1-year postintervention, there were similar improvements as at 3 months, and total PSA levels were significantly reduced by 4% in the intervention group while there was a 6% increase in the control group [58]. Finally, overall health-related quality of life increased in the intervention group compared with the control group [60]. A follow-up for clinical events at 2 years noted that 2 of 43 (5%) patients in the intervention group compared with 13 of 49 (27%) patients in the control group had proceeded to radical PCa treatments [61]. This study provided promising evidence that an intensive lifestyle intervention in PCa patients on AS may slow the progression of the disease, improve some aspects of quality of life and decrease the rate of radical treatments; however, it is unclear whether the benefits were due to diet, exercise or stress management.

Another randomised controlled trial in 26 men with PCa undergoing AS tested the effects of a 6-month combined whole-grain diet and vigorous exercise programme [63]. The exercise programme included non-supervised aerobic exercise 3 times/week of 45 min/session targeting 70% of maximal HR, in addition to at least 10,000 steps daily. The combined intervention resulted in a significant improvement in VO_{2peak} compared with the control group but no significant differences in body composition, cardiometabolic outcomes or PSA levels. Moreover, several cohort, cross-sectional and systematic review studies have also suggested the potential roles of lifestyle characteristics for cancer-related outcomes [63-66], however, the isolated

effects of exercise during AS on physical fitness, fear of cancer progression or PCa-related outcomes were not investigated.

More recently, one completed and one ongoing trial, focused on exercise in PCa patients on AS, have been reported. Bourke et al conducted an exercise clinical trial on 50 PCa patients undergoing AS [67]. The exercise programme included supervised exercise training sessions with behavioural support, targeting 150 min of moderate to vigorous exercise per week over 12 months. Although preliminary, the findings suggest exercise is a feasible and acceptable intervention during AS. Also, Galvão and colleagues have reported the protocol for a 3-year long randomised trial examining the effects of a long-term aerobic and resistance exercise programme on the need for invasive treatment [68]. Compared with these two studies, the ERASE trial will address the efficacy of a relatively shorter term (ie, 12 weeks) high-intensity aerobic exercise on various clinically-relevant outcomes including tumour-related biomarkers, fear of cancer progression and disease progression outcomes.

Our primary outcome of cardiorespiratory fitness was selected for the following reasons. First, evidence shows that improvement in cardiorespiratory fitness is inversely correlated with prostate-specific antigen doubling time ($R2=0.41$, $p<0.003$), which is one of the indicators of biochemical and clinical progression of PCa [18]. These data suggest that improvement in cardiorespiratory fitness through aerobic training induces systemic and physiological changes that may interact with molecular suppression of cancer progression [18]. It is also supported by epidemiological studies showing inverse association between cardiorespiratory fitness and development of PCa [69, 70]. In addition, cardiorespiratory fitness has important clinical implications for cardiovascular and overall prognosis of PCa [69]. PCa patients are at a higher risk of cardiovascular morbidity [71, 72], and mortality [72, 73], and are three times more likely

to die of cardiovascular disease than of PCa [6]. Cardiorespiratory fitness is an established surrogate marker for cardiovascular disease and overall survival [74, 75], and impaired cardiopulmonary fitness, commonly reported among cancer patients, is correlated with cancer-related symptoms and clinical outcomes [76]. Thus, maintaining or improving cardiopulmonary fitness is of clinical importance in PCa patients on AS [76].

We elected to test a HIIT exercise intervention for several reasons. In terms of maximising the potential benefits of exercise in AS patients, a body of evidence supports the thesis that higher-intensity exercise programmes often produce greater health benefits compared with moderate-intensity continuous training [77-81]. HIIT aerobic exercise is a type of high-intensity exercise, alternating short periods of intense exercise and active recovery. HIIT has been shown to induce greater physical and physiological, health-related outcomes such as improvements in cardiorespiratory fitness and cardiovascular disease risk factors compared with traditional moderate-intensity exercise in patient with heart disease [80-83], and cancer [84]. Also, in terms of the tumour microenvironment, higher-intensity exercise seems to be required to induce a sufficient increase in NK cell infiltration to kill tumour cells (up to 60% in animal models) [23], with other potential anticancer properties (eg, modulating inflammation, oxidative stress, lactate and insulin resistance) [85, 86]. Finally, HIIT has been tested in several types of cancer patients and is not only feasible and safe [87-91], but also provides better physiological and psychosocial outcomes [84, 92], exercise adherence [84, 92, 93], and cost-effectiveness [93].

Our model (**Figure 2-1**) proposes that a sufficiently delivered dose and intensity of exercise, indicated by improvement in cardiorespiratory fitness, may benefit men with PCa on AS through three distinct pathways: (1) In the ‘biological pathway’, exercise may have a direct effect on suppressing tumour growth, thereby, delaying or preventing the need for radical

treatments in AS patients. Scientific evidence shows that exercise can modulate cancer-related circulating markers in various mechanisms [94-97], such as immune functions (eg, NK cell mobilisation and infiltration into cancer cells) [98-101], inflammation (eg, systemic concentrations of IL-6, TNF-α and CRP) [102], and metabolism (eg, insulin and IGF-axis) [19, 22], which creates an antitumour microenvironment resulting in a delay or even reversing of tumour progression [97]. (2) In the 'psychological pathway', exercise may reduce the fear of cancer progression through several psychological mechanisms such as providing a distraction and a sense of control, reducing anxiety/cancer worry and intrusive thoughts and providing an alternative explanation for everyday symptoms such as mild pain, fatigue and soreness that may be misinterpreted as signs of cancer progression [12, 13]. These psychological benefits may also improve quality of life and prevent these men from requesting radical treatments as a way of managing their anxiety and fear of cancer progression. (3) In the 'functional pathway', exercise can improve overall physical function, aerobic fitness, muscular strength, body composition and activities of daily living. Improvements in these factors may help reduce the impact and complications of radical treatments and improve long-term prognosis. If PCa patients on AS feel they are better prepared physically for radical treatments and that they will experience fewer side effects and complications, they may also reduce their fear of cancer progression.

There are several strengths of the ERASE trial. It will be one of the few exercise oncology studies in the AS setting to evaluate the isolated effects of exercise. Previous exercise studies in PCa patients have focused on patients during or after treatments, particularly androgen deprivation therapy. Findings from patients receiving or recovering from active treatments are unable to answer important questions of PCa patients on AS related to disease progression, fear of cancer progression and preparation for treatments. Second, to the best of our knowledge, our

study will be the first clinical trial to evaluate HIIT aerobic exercise in AS patients. Recent exercise oncology studies have tested different exercise intensities (ie, moderate-to-vigorous intensity continuous aerobic exercise) [67, 68], modalities (ie, aerobic and resistance combined) [68], or settings (ie, supervised plus home-based) [67], which may have different impacts on physiological and psychosocial responses as well as on feasibility outcomes. Based on up-to-date evidence in exercise oncology, HIIT aerobic exercise can be safe and feasible in this population and may be a superior modality for improving tumour suppression and clinical outcomes. Third, ERASE will be the first exercise randomised controlled trial to examine fear of cancer progression as an outcome. This psychological construct has emerged as a major unmet need in the psychological management of cancer patients and, especially in the AS setting, it has been proposed that it may actually influence treatment decisions. ERASE will provide evidence whether patient-reported fear of cancer progression can be modulated by HIIT exercise. Fourth, ERASE will explore the effects of exercise on potential cancer-related outcomes. Recent epidemiological and preclinical evidence suggests a positive association between exercise and PCa survival and a potential biological link between exercise and tumour growth and metastasis [97]; however, this question has not been studied in a clinical setting. We will assess cancer-related biomarkers as well as immune, metabolic, inflammatory and sex hormones to identify exploratory evidence of the potential antitumour mechanisms of exercise. Also, we will follow-up with participant medical records to document progression to radical treatment up to 1 year. Limitations of the ERASE trial include the lack of ability to blind participants and interventionists to group allocation, the self-selection sampling bias, the relatively short periods of intervention and follow-up and insufficient power to examine clinical outcomes.

In summary, the ERASE trial is expected to provide preliminary evidence that exercise improves physical fitness, manages fear of cancer progression and suppresses tumour-progression related biomarkers in men with PCa receiving AS. This study will advance knowledge and inform larger phase II and III trials designed to determine the effects of exercise on clinically important outcomes in this patient population, including progression to radical treatments, short-term complications after radical treatment and long-term outcomes related to recurrence, metastasis and overall survival. If exercise can be shown to suppress tumour progression, reduce fear of cancer progression and help men with PCa remain on AS longer, it would represent a critical advancement in the treatment and care of PCa patients receiving AS.

Ethics and dissemination

The ultimate purpose of the ERASE trial is to change AS clinical practice by disseminating our findings to clinicians and cancer organisations involved in the care of patients. We will disseminate our findings to these groups including presentations at annual conferences and publications in scientific journals that have a clinical focus. Also, we will directly educate PCa patients and their families about our research findings by actively using media, educational materials, and outreach to hospitals and patient advocacy groups as it is crucial to educate AS patients on the potential benefits of exercise on their physiological and psychological health and encourage them to eventually participate in exercise.

2.5 Reference

1. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al., EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol*, 2011. **59**(1): p. 61-71.
2. Talcott JA, Rieker P, Clark JA, Propert KJ, Weeks JC, Beard CJ, et al., Patient-reported symptoms after primary therapy for early prostate cancer: results of a prospective cohort study. *J Clin Oncol*, 1998. **16**(1): p. 275-83.
3. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al., Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1425-37.
4. Chen RC, Basak R, Meyer AM, Kuo TM, Carpenter WR, Agans RP, et al., Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. *JAMA*, 2017. **317**(11): p. 1141-50.
5. Cooperberg MR, Carroll PR, and Klotz L, Active surveillance for prostate cancer: progress and promise. *J Clin Oncol*, 2011. **29**(27): p. 3669-76.
6. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al., 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1415-24.
7. Dall'Era MA, The economics of active surveillance for prostate cancer. *Curr Opin Urol*, 2013. **23**(3): p. 278-82.

8. Keegan KA, Dall'Era MA, Durbin-Johnson B, and Evans CP, Active surveillance for prostate cancer compared with immediate treatment: an economic analysis. *Cancer*, 2012. **118**(14): p. 3512-8.

9. Lao C, Edlin R, Rouse P, Brown C, Holmes M, Gilling P, et al., The cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for low risk localised prostate cancer. *BMC Cancer*, 2017. **17**(1): p. 529.

10. Dragomir A, Cury FL, and Aprikian AG, Active surveillance for low-risk prostate cancer compared with immediate treatment: a Canadian cost comparison. *CMAJ Open*, 2014. **2**(2): p. E60-8.

11. Marzouk K, Assel M, Ehdaie B, and Vickers A, Long-Term Cancer Specific Anxiety in Men Undergoing Active Surveillance of Prostate Cancer: Findings from a Large Prospective Cohort. *J Urol*, 2018. **200**(6): p. 1250-5.

12. Wallace M, Uncertainty and quality of life of older men who undergo watchful waiting for prostate cancer. *Oncol Nurs Forum*, 2003. **30**(2): p. 303-9.

13. Parker PA, Davis JW, Latini DM, Baum G, Wang X, Ward JF, et al., Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with favourable-risk prostate cancer undergoing active surveillance. *BJU Int*, 2016. **117**(3): p. 469-77.

14. Kinsella N, Stattin P, Cahill D, Brown C, Bill-Axelson A, Bratt O, et al., Factors Influencing Men's Choice of and Adherence to Active Surveillance for Low-risk Prostate Cancer: A Mixed-method Systematic Review. *Eur Urol*, 2018. **74**(3): p. 261-80.

15. Matthew AG, Raz O, Currie KL, Louis AS, Jiang H, Davidson T, et al., Psychological distress and lifestyle disruption in low-risk prostate cancer patients: Comparison between active surveillance and radical prostatectomy. *J Psychosoc Oncol*, 2018. **36**(2): p. 159-74.

16. Latini DM, Hart SL, Knight SJ, Cowan JE, Ross PL, Duchane J, et al., The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. *J Urol*, 2007. **178**(3 Pt 1): p. 826-31; discussion 31-2.

17. van den Bergh RC, Korfage IJ, and Bangma CH, Psychological aspects of active surveillance. *Curr Opin Urol*, 2012. **22**(3): p. 237-42.

18. Hvid T, Lindegaard B, Winding K, Iversen P, Brasso K, Solomon TP, et al., Effect of a 2-year home-based endurance training intervention on physiological function and PSA doubling time in prostate cancer patients. *Cancer Causes Control*, 2016. **27**(2): p. 165-74.

19. Leung PS, Aronson WJ, Ngo TH, Golding LA, and Barnard RJ, Exercise alters the IGF axis in vivo and increases p53 protein in prostate tumor cells in vitro. *J Appl Physiol (1985)*, 2004. **96**(2): p. 450-4.

20. Jones LW, Antonelli J, Masko EM, Broadwater G, Lascola CD, Fels D, et al., Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. *J Appl Physiol (1985)*, 2012. **113**(2): p. 263-72.

21. McCullough DJ, Nguyen LM, Siemann DW, and Behnke BJ, Effects of exercise training on tumor hypoxia and vascular function in the rodent preclinical orthotopic prostate cancer model. *J Appl Physiol (1985)*, 2013. **115**(12): p. 1846-54.

22. Rundqvist H, Augsten M, Stromberg A, Rullman E, Mijwel S, Kharaziha P, et al., Effect of acute exercise on prostate cancer cell growth. *PLoS One*, 2013. **8**(7): p. e67579.

23. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al., Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. *Cell Metab*, 2016. **23**(3): p. 554-62.

24. Jones LW, Hornsby WE, Freedland SJ, Lane A, West MJ, Moul JW, et al., Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized prostate cancer. *Eur Urol*, 2014. **65**(5): p. 852-5.

25. Cormie P, Newton RU, Spry N, Joseph D, Taaffe DR, and Galvao DA, Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. *Prostate Cancer Prostatic Dis*, 2013. **16**(4): p. 328-35.

26. Cormie P, Galvão DA, Spry N, Joseph D, Chee R, Taaffe DR, et al., Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU international*, 2015. **115**(2): p. 256-66.

27. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al., Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*, 2009. **27**(3): p. 344-51.

28. Galvao DA, Taaffe DR, Spry N, Joseph D, and Newton RU, Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*, 2010. **28**(2): p. 340-7.

29. Park SW, Kim TN, Nam JK, Ha HK, Shin DG, Lee W, et al., Recovery of overall exercise ability, quality of life, and continence after 12-week combined exercise

intervention in elderly patients who underwent radical prostatectomy: a randomized controlled study. *Urology*, 2012. **80**(2): p. 299-305.

30. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, et al., Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol*, 2003. **21**(9): p. 1653-9.

31. Farris MS, Kopciuk KA, Courneya KS, McGregor SE, Wang Q, and Friedenreich CM, Identification and prediction of health-related quality of life trajectories after a prostate cancer diagnosis. *Int J Cancer*, 2017. **140**(7): p. 1517-27.

32. Silver JK and Baima J, Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *Am J Phys Med Rehabil*, 2013. **92**(8): p. 715-27.

33. National Comprehensive Cancer Network (NCCN), *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer*. 2017.

34. Warburton DE, Jamnik VK, Bredin SS, Burr J, Charlesworth S, Chilibeck P, et al., The 2011 Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and the Electronic Physical Activity Readiness Medical Examination (ePARmed-X+). *Heal Fit J Canada*, 2011. **4**: p. 24-5.

35. Godin G and Shephard R, Godin leisure-time exercise questionnaire. *Med Sci Sports Exerc*, 1997. **29**(6): p. 36-8.

36. *Alberta Cancer Exercise (ACE) Program*. Available from: https://www.albertacancerexercise.com/.

37. McInnis KJ and Balady GJ, Comparison of submaximal exercise responses using the Bruce vs modified Bruce protocols. *Med Sci Sports Exerc*, 1994. **26**(1): p. 103-7.

38. Burdon JG, Juniper EF, Killian KJ, Hargreave FE, and Campbell EJ, The perception of breathlessness in asthma. *Am Rev Respir Dis*, 1982. **126**(5): p. 825-8.

39. Simard S and Savard J, Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. *Support Care Cancer*, 2009. **17**(3): p. 241-51.

40. Custers JA, van den Berg SW, van Laarhoven HW, Bleiker EM, Gielissen MF, and Prins JB, The Cancer Worry Scale: detecting fear of recurrence in breast cancer survivors. *Cancer Nurs*, 2014. **37**(1): p. E44-50.

41. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al., The European-Organization-for-Research-and-Treatment-of-Cancer Qlq-C30 - a Quality-of-Life Instrument for Use in International Clinical-Trials in Oncology. *Journal of the National Cancer Institute*, 1993. **85**(5): p. 365-76.

42. Spielberger CD, *State-Trait anxiety inventory*. 2010: Wiley Online Library.

43. Roth AJ, Rosenfeld B, Kornblith AB, Gibson C, Scher HI, Curley-Smart T, et al., The memorial anxiety scale for prostate cancer: validation of a new scale to measure anxiety in men with with prostate cancer. *Cancer*, 2003. **97**(11): p. 2910-8.

44. Lewinsohn PM, Seeley JR, Roberts RE, and Allen NB, Center for epidemiologic studies depression scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychology and Aging*, 1997. **12**(2): p. 277-87.

45. Yellen SB, Cella DF, Webster K, Blendowski C, and Kaplan E, Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*, 1997. **13**(2): p. 63-74.

46. Cohen S, Kamarck T, and Mermelstein R, Perceived stress scale. *Measuring stress: A guide for health and social scientists*, 1994.

47. Rosenberg M, Rosenberg self-esteem scale (RSE). *Acceptance and commitment therapy. Measures package*, 1965. **61**: p. 52.

48. Ajzen I, The theory of planned behavior. *Organizational behavior and human decision processes*, 1991. **50**(2): p. 179-211.

49. Rikli RE and Jones CJ, *Senior fitness test manual*. 2013: Human Kinetics.

50. American College of Sports Medicine, *ACSM's guidelines for exercise testing and prescription*. 2013: Lippincott Williams & Wilkins.

51. Borm GF, Fransen J, and Lemmens WA, A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol*, 2007. **60**(12): p. 1234-8.

52. Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, and Fairey AS, Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *J Clin Oncol*, 2003. **21**(9): p. 1660-8.

53. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al., Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol*, 2007. **25**(28): p. 4396-404.

54. Courneya KS, Sellar CM, Stevinson C, McNeely ML, Peddle CJ, Friedenreich CM, et al., Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J Clin Oncol*, 2009. **27**(27): p. 4605-12.

55. Norris MK, Bell GJ, North S, and Courneya KS, Effects of resistance training frequency on physical functioning and quality of life in prostate cancer survivors: a pilot randomized controlled trial. *Prostate Cancer Prostatic Dis*, 2015. **18**(3): p. 281-7.

56. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, and Conde JGJJobi, Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. 2009. **42**(2): p. 377-81.

57. Royston P, Multiple imputation of missing values. *Stata journal*, 2004. **4**(3): p. 227-41.

58. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al., Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*, 2005. **174**(3): p. 1065-9; discussion 9-70.

59. Ornish DM, Lee KL, Fair WR, Pettengill EB, and Carroll PR, Dietary trial in prostate cancer: Early experience and implications for clinical trial design. *Urology*, 2001. **57**(4 Suppl 1): p. 200-1.

60. Daubenmier JJ, Weidner G, Marlin R, Crutchfield L, Dunn-Emke S, Chi C, et al., Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance. *Urology*, 2006. **67**(1): p. 125-30.

61. Ornish D, Lin J, Daubenmier J, Weidner G, Epel E, Kemp C, et al., Increased telomerase activity and comprehensive lifestyle changes: a pilot study. *Lancet Oncol*, 2008. **9**(11): p. 1048-57.

62. Frattaroli J, Weidner G, Dnistrian AM, Kemp C, Daubenmier JJ, Marlin RO, et al., Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology*, 2008. **72**(6): p. 1319-23.

63. Eriksen AK, Hansen RD, Borre M, Larsen RG, Jensen JM, Overgaard K, et al., A lifestyle intervention among elderly men on active surveillance for non-aggressive prostate cancer: a randomised feasibility study with whole-grain rye and exercise. *Trials*, 2017. **18**(1): p. 20.

64. Kenfield SA, Chang ST, and Chan JM, Diet and lifestyle interventions in active surveillance patients with favorable-risk prostate cancer. *Curr Treat Options Oncol*, 2007. **8**(3): p. 173-96.

65. Burton AJ, Martin RM, Donovan JL, Lane JA, Davis M, Hamdy FC, et al., Associations of lifestyle factors and anthropometric measures with repeat PSA levels during active surveillance/monitoring. *Cancer Epidemiol Biomarkers Prev*, 2012. **21**(10): p. 1877-85.

66. Vandersluis AD, Guy DE, Klotz LH, Fleshner NE, Kiss A, Parker C, et al., The role of lifestyle characteristics on prostate cancer progression in two active surveillance cohorts. *Prostate Cancer Prostatic Dis*, 2016. **19**(3): p. 305-10.

67. Bourke L, Stevenson R, Turner R, Hooper R, Sasieni P, Greasley R, et al., Exercise training as a novel primary treatment for localised prostate cancer: a multi-site randomised controlled phase II study. *Sci Rep*, 2018. **8**(1): p. 8374.

68. Galvao DA, Hayne D, Frydenberg M, Chambers SK, Taaffe DR, Spry N, et al., Can exercise delay transition to active therapy in men with low-grade prostate cancer? A multicentre randomised controlled trial. *BMJ Open*, 2018. **8**(4): p. e022331.

69. Lakoski SG, Willis BL, Barlow CE, Leonard D, Gao A, Radford NB, et al., Midlife Cardiorespiratory Fitness, Incident Cancer, and Survival After Cancer in Men: The Cooper Center Longitudinal Study. *JAMA Oncol*, 2015. **1**(2): p. 231-7.

70. Oliveria SA, Kohl HW, 3rd, Trichopoulos D, and Blair SN, The association between cardiorespiratory fitness and prostate cancer. *Med Sci Sports Exerc*, 1996. **28**(1): p. 97-104.

71. Van Hemelrijck M, Garmo H, Holmberg L, Ingelsson E, Bratt O, Bill-Axelson A, et al., Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. *J Clin Oncol*, 2010. **28**(21): p. 3448-56.

72. Gupta D, Lee Chuy K, Yang JC, Bates M, Lombardo M, and Steingart RM, Cardiovascular and Metabolic Effects of Androgen-Deprivation Therapy for Prostate Cancer. *J Oncol Pract*, 2018. **14**(10): p. 580-7.

73. Matthes KL, Pestoni G, Korol D, Van Hemelrijck M, and Rohrmann S, The risk of prostate cancer mortality and cardiovascular mortality of nonmetastatic prostate cancer patients: A population-based retrospective cohort study. *Urol Oncol*, 2018. **36**(6): p. 309 e15- e23.

74. Myers J, Prakash M, Froelicher V, Do D, Partington S, and Atwood JE, Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*, 2002. **346**(11): p. 793-801.

75. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al., Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*, 2009. **301**(19): p. 2024-35.

76. Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS, et al., Efficacy of Exercise Therapy on Cardiorespiratory Fitness in Patients With Cancer: A Systematic Review and Meta-Analysis. *J Clin Oncol*, 2018. **36**(22): p. 2297-305.

77. Helgerud J, Hoydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, et al., Aerobic high-intensity intervals improve VO2max more than moderate training. *Medicine and Science in Sports and Exercise*, 2007. **39**(4): p. 665-71.

78. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, and Coombes JS, The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. *Sports Med*, 2015. **45**(5): p. 679-92.

79. Gibala MJ, Little JP, Macdonald MJ, and Hawley JA, Physiological adaptations to low-volume, high-intensity interval training in health and disease. *J Physiol*, 2012. **590**(5): p. 1077-84.

80. Cardozo GG, Oliveira RB, and Farinatti PT, Effects of high intensity interval versus moderate continuous training on markers of ventilatory and cardiac efficiency in coronary heart disease patients. *ScientificWorldJournal*, 2015. **2015**: p. 192479.

81. Weston KS, Wisloff U, and Coombes JS, High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med*, 2014. **48**(16): p. 1227-34.

82. Warburton DE, McKenzie DC, Haykowsky MJ, Taylor A, Shoemaker P, Ignaszewski AP, et al., Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *Am J Cardiol*, 2005. **95**(9): p. 1080-4.

83. Moholdt TT, Amundsen BH, Rustad LA, Wahba A, Lovo KT, Gullikstad LR, et al., Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *Am Heart J*, 2009. **158**(6): p. 1031-7.

84. Toohey K, Pumpa K, McKune A, Cooke J, and Semple S, High-intensity exercise interventions in cancer survivors: a systematic review exploring the impact on health outcomes. *J Cancer Res Clin Oncol*, 2018. **144**(1): p. 1-12.

85. Papadopoulos E and Santa Mina D, Can we HIIT cancer if we attack inflammation? *Cancer Causes Control*, 2018. **29**(1): p. 7-11.

86. Hofmann P, Cancer and Exercise: Warburg Hypothesis, Tumour Metabolism and High-Intensity Anaerobic Exercise. *Sports (Basel)*, 2018. **6**(1).

87. Banerjee S, Manley K, Shaw B, Lewis L, Cucato G, Mills R, et al., Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a feasibility randomised controlled trial. *Support Care Cancer*, 2018. **26**(5): p. 1515-23.

88. Licker M, Karenovics W, Diaper J, Fresard I, Triponez F, Ellenberger C, et al., Short-Term Preoperative High-Intensity Interval Training in Patients Awaiting Lung Cancer Surgery: A Randomized Controlled Trial. *J Thorac Oncol*, 2017. **12**(2): p. 323-33.

89. Schmitt J, Lindner N, Reuss-Borst M, Holmberg HC, and Sperlich B, A 3-week multimodal intervention involving high-intensity interval training in female cancer survivors: a randomized controlled trial. *Physiol Rep*, 2016. **4**(3).

90. Schulz SVW, Laszlo R, Otto S, Prokopchuk D, Schumann U, Ebner F, et al., Feasibility and effects of a combined adjuvant high-intensity interval/strength training in breast cancer patients: a single-center pilot study. *Disabil Rehabil*, 2018. **40**(13): p. 1501-8.

91. Toohey K, Pumpa KL, Arnolda L, Cooke J, Yip D, Craft PS, et al., A pilot study examining the effects of low-volume high-intensity interval training and continuous low to moderate intensity training on quality of life, functional capacity and cardiovascular risk factors in cancer survivors. *PeerJ*, 2016. **4**: p. e2613.

92. Adams SC, DeLorey DS, Davenport MH, Stickland MK, Fairey AS, North S, et al., Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: A phase 2 randomized controlled trial. *Cancer*, 2017. **123**(20): p. 4057-65.

93. Kampshoff CS, van Dongen JM, van Mechelen W, Schep G, Vreugdenhil A, Twisk JWR, et al., Long-term effectiveness and cost-effectiveness of high versus low-to-moderate intensity resistance and endurance exercise interventions among cancer survivors. *J Cancer Surviv*, 2018. **12**(3): p. 417-29.

94. Hayes BD, Brady L, Pollak M, and Finn SP, Exercise and Prostate Cancer: Evidence and Proposed Mechanisms for Disease Modification. *Cancer Epidemiol Biomarkers Prev*, 2016. **25**(9): p. 1281-8.

95. Ruiz-Casado A, Martin-Ruiz A, Perez LM, Provencio M, Fiuza-Luces C, and Lucia A, Exercise and the Hallmarks of Cancer. *Trends Cancer*, 2017. **3**(6): p. 423-41.

96. Hojman P, Gehl J, Christensen JF, and Pedersen BK, Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. *Cell Metab*, 2018. **27**(1): p. 10-21.

97. Ashcraft KA, Peace RM, Betof AS, Dewhirst MW, and Jones LW, Efficacy and Mechanisms of Aerobic Exercise on Cancer Initiation, Progression, and Metastasis: A Critical Systematic Review of In Vivo Preclinical Data. *Cancer Res*, 2016. **76**(14): p. 4032-50.

98. Bigley AB and Simpson RJ, NK cells and exercise: implications for cancer immunotherapy and survivorship. *Discov Med*, 2015. **19**(107): p. 433-45.

99. Idorn M and Hojman P, Exercise-Dependent Regulation of NK Cells in Cancer Protection. *Trends Mol Med*, 2016. **22**(7): p. 565-77.

100. Idorn M and Thor Straten P, Exercise: A new role for an old tool. *Mol Cell Oncol*, 2016. **3**(4): p. e1163005.

101. Simpson RJ, Bigley AB, Agha N, Hanley PJ, and Bollard CM, Mobilizing Immune Cells With Exercise for Cancer Immunotherapy. *Exerc Sport Sci Rev*, 2017. **45**(3): p. 163-72.

102. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, and Nimmo MA, The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*, 2011. **11**(9): p. 607-15.

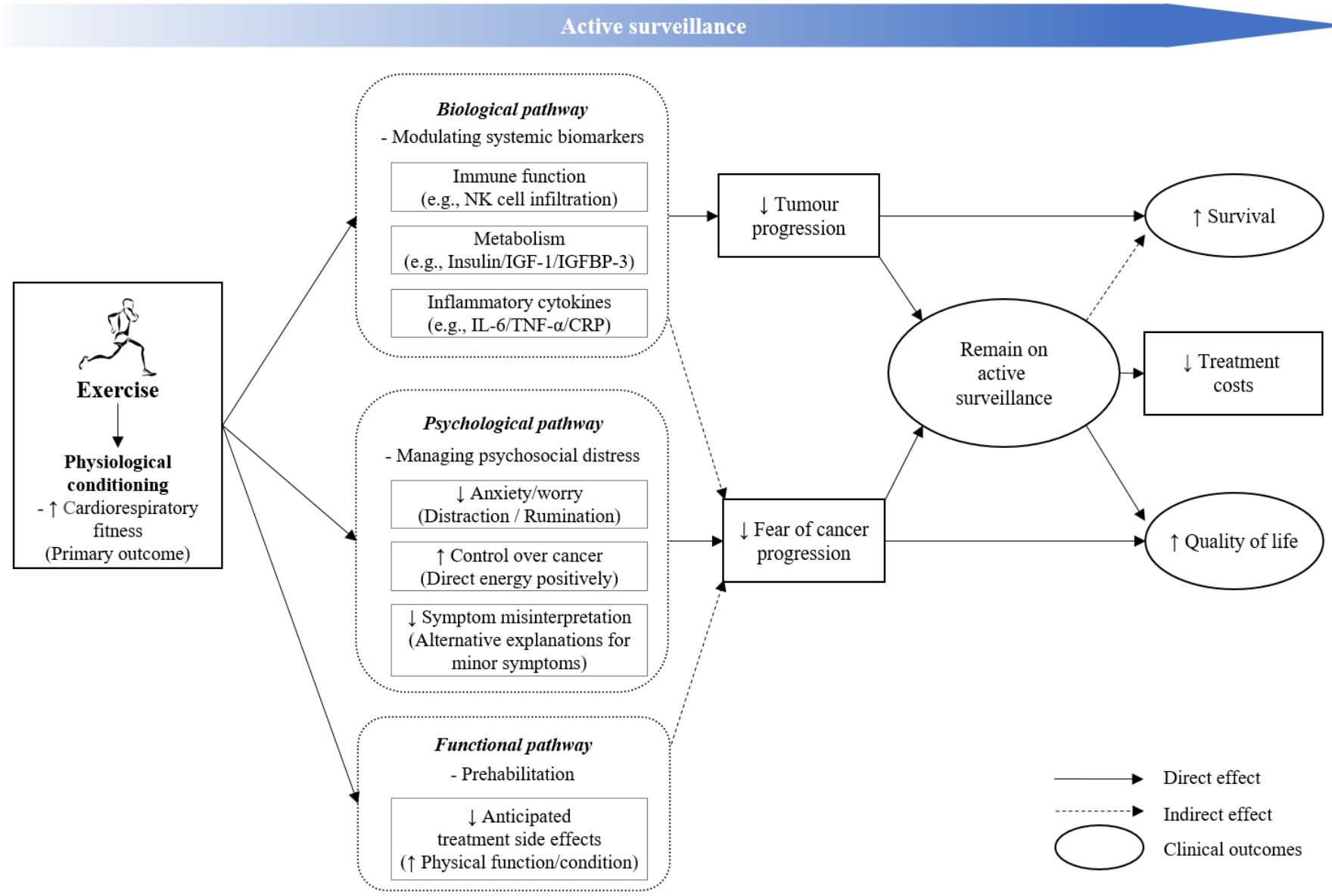
Table 2-1. Study activities/assessments schedule based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

Activity/assessment	Staff member	Approx. time to complete	T_{-1} Screening/ consent	T_0 Baseline assessment/ randomization	T_1 Start intervention	T_2 End intervention	T_3 Post-intervention assessment	F_1 6-momth Follow-up	F_2 Follow-up 1-year
ENROLMENT									
Eligibility screen	Study coordinator	5 mins	X						
Informed consent	Study coordinator	5 mins	X						
Randomization	Study coordinator	5 mins		X					
INTERVENTIONS									
Exercise training	CEPs	30 mins per session			◆—	—◆			
Usual care	N/A	N/A			◆—	—◆			
ASSESSMENTS									
Demographic/behavioral /medical variables	Study coordinator	5 mins		X					
Primary outcome									
Cardiorespiratory fitness	CEPs	20 mins		X			X		
Secondary outcomes									
Physical function/ anthropometrics	CEPs	20 mins		X			X		
Blood biomarkers	Lab technicians	15 mins		X			X		
PSA	Lab technicians	15 mins		X			X	X	X
Patient reported outcomes	Study coordinator	30 mins		X			X	X	X
Exploratory outcomes									
Clinical events	Study coordinator	5 mins		X			X	X	X

CEP, clinical exercise physiologist; PSA, prostate specific antigen

Table 2-2. The 12-week high-intensity interval training (HIIT) periodization scheme and program details in the ERASE trial.

Intervention Period	Week	Warm-up	High-intensity phase				Recovery phase				Cool-down	Total duration (min)
			Intensity (VO_{2peak})	Duration (min)	No. intervals	Sum high-intensity duration (min)	Intensity (VO_{2peak})	Duration (min)	No. intervals	Sum recovery duration (min)		
Period 1	1-4	5 mins at 60% VO_{2peak}	85%	2	5-8	10-16	40%	2	4-7	8-14	5 mins at 30% VO_{2peak}	28-40
Period 2	5-8		90%	2	8	16	40%	2	7	14		40
Period 3	9-12		95%	2	8	16	40%	2	7	14		40



NK cell, natural killer cell; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; IL, interleukin; TNF, tumor necrosis factor; CRP, c-reactive protein

Figure 2-1. Proposed effects of exercise during active surveillance in prostate cancer patients

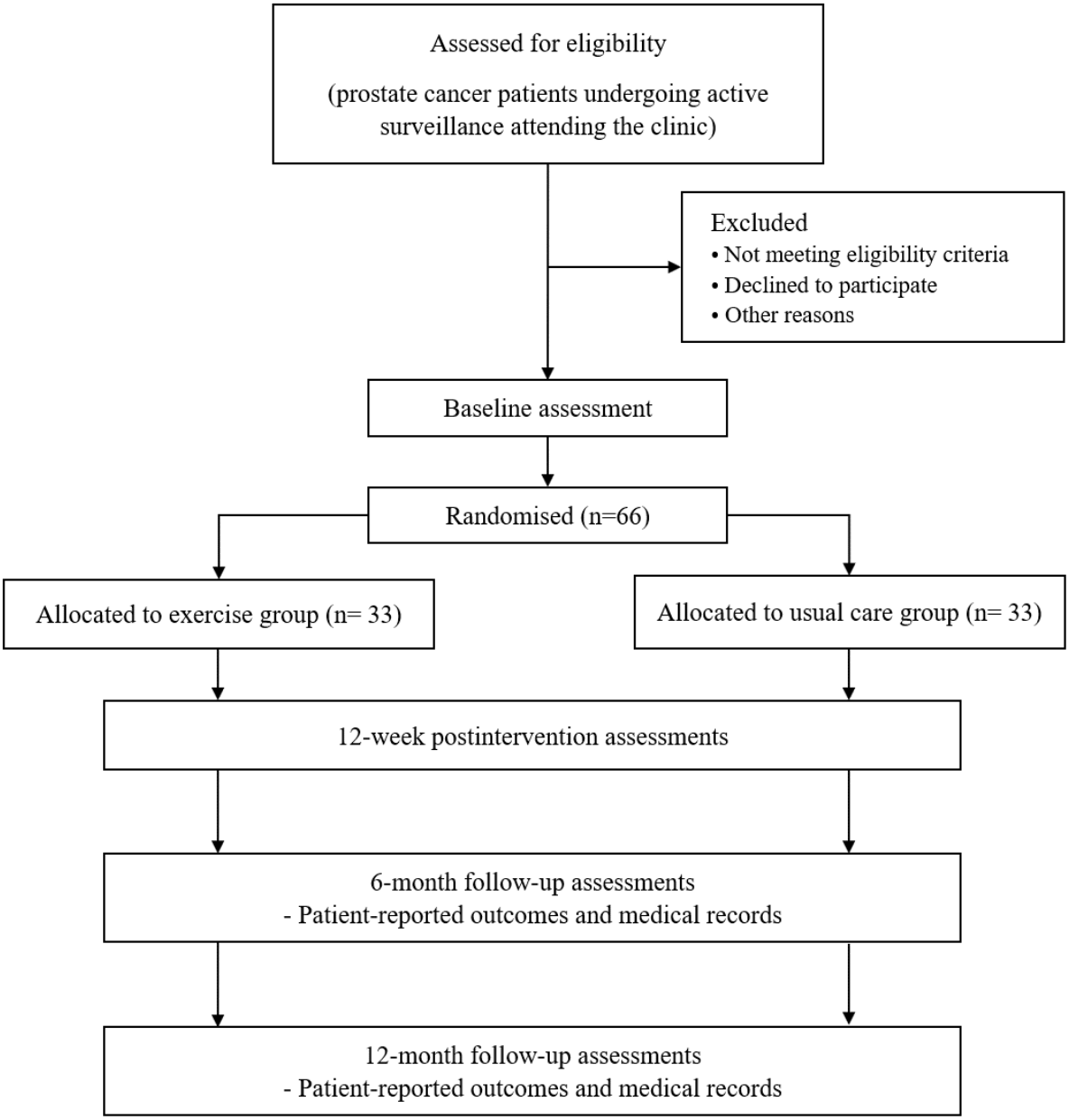


Figure 2-2. Proposed patient flow diagram of the ERASE trial

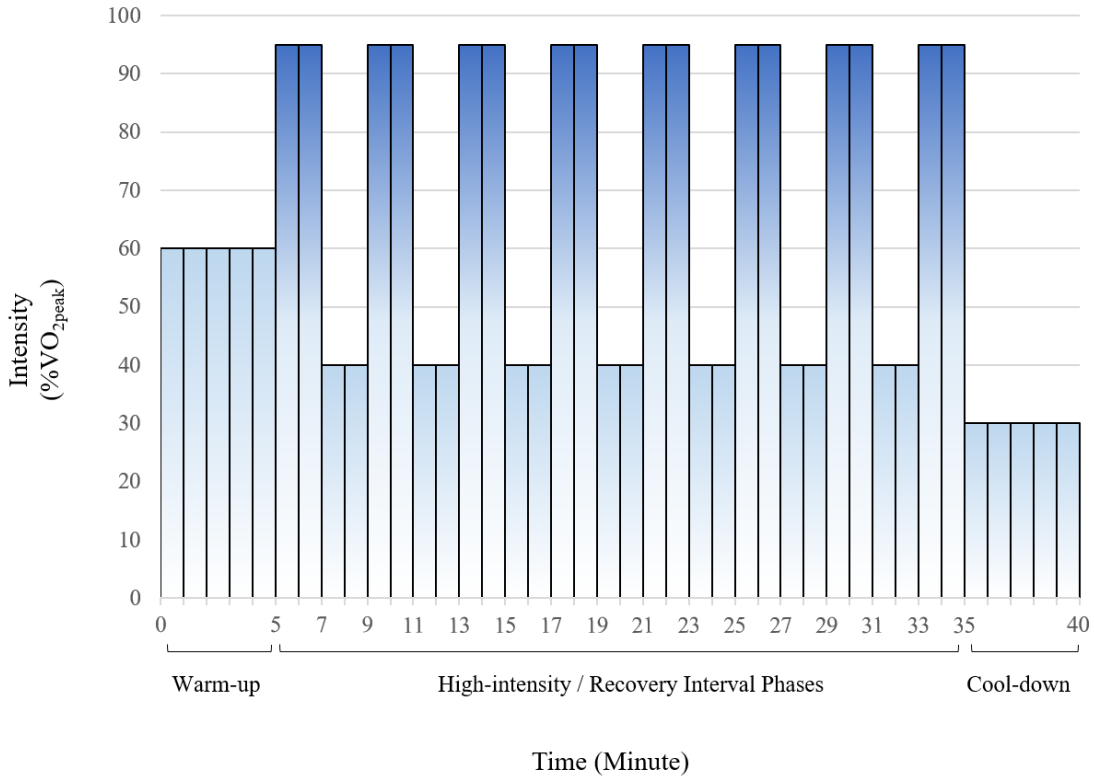


Figure 2-3. High-intensity interval training (HIIT) program in the ERASE trial.

CHAPTER 3 – PAPER 2 (Primary Outcomes)

Effects of high-intensity interval training on physical fitness and prostate-specific antigen in prostate cancer patients on active surveillance: A randomized controlled trial

3.1 Abstract

Background: Men with low-risk localized prostate cancer are often managed with active surveillance (AS) to avoid treatment side effects. Unfortunately, 30-50% of these men ultimately require radical treatments. Exercise has the potential to suppress prostate cancer progression and pre-habilitate these men to prepare for possible treatment and its side effects; however, few exercise studies have been conducted in the AS setting.

Methods: The Exercise During Active Surveillance for Prostate Cancer (ERASE) Trial was a single-centre, randomized controlled trial, and 52 men with localized prostate cancer on AS were randomized to high-intensity interval training (HIIT; n=26) or usual care (UC; n=26). The HIIT group performed thrice-weekly, supervised, aerobic HIIT on a treadmill at 85-95% of peak cardiorespiratory fitness (VO_{2peak}) for 12 weeks. The primary outcome was VO_{2peak} and the secondary outcomes included biochemical progression of prostate cancer (prostate-specific antigen [PSA]), functional fitness, and anthropometrics.

Results: 46/52 participants (88%) completed the postintervention VO_{2peak} assessment and adherence to HIIT was 96%. Compared to UC, HIIT showed higher VO_{2peak} (adjusted between-group mean difference, 1.6 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% confidence interval [CI], 0.3 to 2.9; p=0.014), lower PSA (adjusted between-group mean difference, -1.1 ug/L; 95% CI, -2.1 to 0.0; p=0.043), lower PSA velocity (p=0.040), better upper body strength (p=0.001), and better lower body flexibility (p=0.042).

Conclusions: ERASE is the first randomized controlled trial to demonstrate that HIIT improves physical fitness and PSA levels in men with localized prostate cancer on AS. Larger trials are warranted to determine if HIIT improves clinical outcomes in men with prostate cancer on AS.

3.2 Introduction

An increasing number of men with low- to intermediate-risk prostate cancer (PCa) choose active surveillance (AS) as their primary management strategy [1]. Advantages of AS include avoiding immediate radical treatment and side effects without compromising survival benefits [2, 3] and a reduction in treatment-related medical costs [4, 5]. Unfortunately, approximately 30% of men on AS will ultimately receive radical treatment within three years and 55% within ten years [2], which accompany side effects such as urinary, hormonal, and sexual dysfunction [6]. Moreover, the risks of cancer progression and metastasis are higher in prostate cancer patients who were on AS compared to those who had undergone radical treatments [2]. Interventions during AS to delay disease progression and precondition these men for impending radical treatments can address this unmet clinical need.

Exercise improves physical fitness, physical functioning, body composition, fatigue, and quality of life during and after radical PCa treatments [7]. Moreover, aerobic exercise has been shown to suppress the progression of prostate tumours and metastasis in animal models [8] and improve biochemical outcomes of prostate cancer growth in human settings [9, 10]. Furthermore, improvements in physical fitness and function during AS may improve treatment side effects and cancer-related outcomes after radical treatments [11, 12]. Therefore, exercise may be a cost-effective intervention that can help these men remain on AS longer and improve physical fitness to prepare them for possible radical treatment and its side effects. To date, however, only one clinical trial has examined the feasibility of exercise in men on AS and none has investigated the efficacy of isolated exercise during AS [13]. The purpose of the Exercise During Active Surveillance for Prostate Cancer (ERASE) Trial [14] was to examine the effects of exercise on cardiopulmonary fitness, physical functioning, anthropometrics, biochemical progression of PCa

(prostate-specific antigen [PSA]), cancer-related biomarkers, and patient-reported outcomes in men with PCa undergoing AS. Here, we report the results for cardiopulmonary fitness, PSA levels and kinetics, physical functioning, and anthropometrics. We hypothesized that, compared to usual care (UC), high-intensity interval training (HIIT) would elicit significant improvements in the primary outcome of cardiopulmonary fitness and the secondary outcomes of physical fitness and biochemical progression of PCa.

3.3 Methods

Participants

The detailed methods of the ERASE Trial have been reported elsewhere [14]. In brief, participants were recruited through the Northern Alberta Urology Centre at the Kaye Edmonton Clinic, Edmonton, Alberta, Canada. Men were eligible if they were (1) ≥18 years old, (2) diagnosed with localized low-to-intermediate risk PCa, (3) undergoing AS with no plans for invasive treatment at the time of recruitment, (4) medically cleared to participate in the study, (5) able to complete the baseline fitness test, (6) not currently participating in vigorous-intensity exercise, (7) willing to be randomized, and (8) able to communicate in English. The ERASE Trial was approved by the Health Research Ethics Board of Alberta – Cancer Committee (HREBA.CC-17-0248) and registered in the ClinicalTrial.gov (NCT03203460). All participants provided written informed consent for study participation and blood banking prior to enrollment.

Study Design and Procedure

The ERASE trial was a single centre, two-armed, phase II randomized controlled trial conducted at the University of Alberta, Edmonton, Canada. Eligible participants were informed about the study by their urologists during their checkup visits and referred to the study coordinator. Interested patients were given detailed study information, and patients who agreed

to participate in the study were scheduled for baseline assessments. Upon the completion of baseline testing, patients were randomly assigned to the HIIT group or UC group in a 1:1 ratio using a 4 or 6 random block design. The allocation sequence was produced by computer-generated block randomization numbers and concealed from study staff involved in recruitment and baseline assessment. Participants and interventionists were not blinded to group assignment. Outcome assessors were not blinded to group assignment for the physical fitness and anthropometric assessments but were blinded for all other secondary outcomes.

Intervention

Participants randomized to the HIIT group were asked to complete a 12-week, thrice-weekly, supervised exercise program. The exercise program was individualized based on each participant's baseline cardiopulmonary fitness, and the intensity and duration were progressed over time. Each exercise session was performed on a treadmill consisting of (1) 5-minute warm-up at 60% of peak oxygen consumption (VO_{2peak}), (2) alternating 2-minute high-intensity interval at 85 to 95% VO_{2peak} and 2-minute active recovery at 40% of VO_{2peak}, and (3) 5-minute cool-down at 30% of VO_{2peak}. Oxygen consumption was not directly measured during the exercise sessions but the treadmill speed and grade were selected to match the targeted % VO_{2peak} based on the baseline fitness levels. The number of high-intensity intervals was progressed from 5 to 8 in each session, and the total duration of the exercise session was progressed from 28 to 40 minutes. At the end of the sessions, participants were asked to complete 2 sets of 15-second stretching on each side of three lower body muscle groups (i.e., quadriceps, hamstrings, and calves) for a total of 3-5 minutes. Participants in the UC group were asked not to change their exercise levels from baseline during the intervention period. After the postintervention

assessments at 12-week, the UC group were offered a 4-week HIIT program at our facility and/or referred to a 12-week community-based exercise program.

Outcome Measures

Primary Outcome

Our primary outcome was cardiorespiratory fitness measured as peak oxygen consumption (VO_{2peak}) and assessed at baseline and postintervention. VO_{2peak} was defined as the highest values of oxygen uptake averaged among every 15-second interval during the graded exercise test using a modified Bruce protocol [15]. The criteria for a valid test included volitional exhaustion as the primary criterion, respiratory exchange ratio (RER)>1.15, age-predicted maximum heart rate (HR) within 5 bpm, and rated perceived exertion (RPE)>7 (0-10 scale) [16]. The test was conducted on a treadmill (Woodway 4Front; Waukesha, WI, USA) with direct measures of gas exchange and cardiorespiratory variables using a metabolic cart (Parvo Medics TrueOne 2400; Sandy, UT, USA). VO_{2peak} is reported in both relative ($ml \cdot kg^{-1} \cdot min^{-1}$) and absolute (L/min) terms.

Secondary Outcomes

Our secondary outcomes included serum PSA levels and kinetics (i.e., PSA doubling time and velocity), functional fitness, and anthropometrics. Blood samples were collected after 12-hour fasting at the Kaye Edmonton Clinic Laboratory Services. Serum PSA levels were analyzed on fresh blood at the central processing facility and the results were available through electronic medical records. Two additional 6 ml blood samples in EDTA tubes were collected for research purposes and sent to the biochemistry lab in the Li Ka Shing Centre for Health Research Innovation at the University of Alberta. PSA doubling time and velocity were calculated following the PSA Working Group Guidelines [17] using the three most recent PSA values

obtained from the medical chart with the first and last values being at least three months apart. The formula was based on the natural logarithm of 2 (0.693) divided by the slope obtained from fitting a linear regression of the natural log of PSA. The calculations were performed using an online tool (https://www.mskcc.org/nomograms/prostate/psa_doubling_time).

Functional fitness was assessed using the Senior's Fitness Test [18] measuring lower body strength (chair stand), upper body strength (arm curl), lower body flexibility (chair sit and reach), upper body flexibility (back scratch), agility (8-foot up and go) and aerobic fitness (6-min walk test). Anthropometrics included weight, height, and waist and hip circumferences using scales and tape measures following the standardized protocols [19].

Demographic, Behavioural, and Medical Variables

Demographic and behavioural information was obtained using a self-reported questionnaire at baseline including age, ethnicity, education, marital status, income, employment status, smoking, alcohol consumption, and exercise behaviour [20]. Patients' medical information was extracted from the electronic medical record including tumour pathology and clinical stage.

Statistical Analyses and Sample Size Calculation

A sample size of 66 participants (33 per group) was estimated to provide 80% power using a two-tailed alpha <0.05 to detect a statistically significant between-group difference of 1-metabolic equivalent task (1-MET=3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) on our primary outcome of VO_{2peak}, assuming a SD of 5.6 $ml \cdot kg^{-1} \cdot min^{-1}$, 10% dropout rate, and adjustment for baseline value and other covariates [21]. This sample size was also sufficient for detecting differences in our secondary outcomes of biomarkers, functional fitness, and anthropometrics. Analyses of covariance were performed for the primary and secondary outcomes to compare the between-

group mean differences at postintervention after adjusting for covariates. Covariates were selected a priori and included baseline values of the outcome and other covariates that were unbalanced between groups, such as smoking, BMI, and physical activity levels. All statistical analyses included all study participants who had baseline and follow-up data using the intention-to-treat method. No missing data strategy was employed and no adjustment was made for multiple comparisons due to a minimal loss of data (<10%).

3.4 Results

Participant Flow

The study participant flow is illustrated in **Figure 3-1**. Participants were recruited from July 2018 to February 2020. Overall, 361 men with PCa undergoing AS were screened, 176 (51%) were eligible, and 52 (30%) were randomized with 26 participants per group. There were two dropouts from the HIIT group (unwillingness; medical issue) and one from the UC group (no contact). A total of 46 participants (88%) completed the postintervention VO_{2peak} assessment and 49 (94%) completed the postintervention functional fitness assessment and blood draw.

Baseline Characteristics and Intervention Adherence

Demographic, medical, and behavioural characteristics of the participants at baseline are presented in **Table 3-1**. Baseline exercise behaviours were unbalanced between groups and adjusted for in the analyses because of their prognostic association with PSA [22, 23] and fitness outcomes [24]. Due to the outbreak of COVID-19 and the impending closure of our exercise and testing facilities, we completed postintervention assessments two weeks earlier than planned (i.e., 10 weeks) for the last 6 participants (3 in each group) in order to minimize the loss of data. The total number of attended sessions was 880/918 (96%) with 100% compliance to the

intervention protocol (i.e., intensity and duration). 8 participants reported aggravation of previous medical issues including joint pain (n=6), chest discomfort (n=1), and light-headedness (n=1) that were potentially related to HIIT and one reported stomach bleeding of Dieulafoy lesion that was not related to HIIT.

Primary and Secondary Outcomes

Changes in cardiopulmonary fitness, physical function, and anthropometric outcomes are presented in **Table 3-2**. The primary outcome of VO_{2peak} increased by 0.9 $ml \cdot kg^{-1} \cdot min^{-1}$ in the HIIT group and decreased by 0.5 $ml \cdot kg^{-1} \cdot min^{-1}$ in the UC group (adjusted between-group mean difference, 1.6 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% confidence interval [CI], 0.3 to 2.9; p=0.014). Compared to the UC group, the HIIT group also significantly increased VO_{2peak} in L/min (p=0.026). For functional fitness, the HIIT group improved upper body strength (p=0.001) and lower body flexibility (p=0.042) compared to the UC group. No statistically significant between-group differences were found for other functional fitness and anthropometric outcomes.

Changes in PSA levels, doubling time, and velocity are shown in **Table 3-3** and **Figure 3-2**. Compared to the UC group, the HIIT group showed a significant reduction in PSA levels (adjusted between-group mean difference, -1.1 ug/L; 95% CI, -2.1 to 0.0; p=0.043) and PSA velocity (adjusted between-group mean difference, -1.3 $ug \cdot L^{-1} \cdot year^{-1}$; 95% CI, -2.5 to -0.1; p=0.040). PSA doubling time favoured the HIIT group but did not reach statistical significance (adjusted between-group mean difference, 17.9 months; 95% CI, -3.8 to 39.6; p=0.10). There was no between-group difference in testosterone (p=0.24).

3.5 Discussion

To our knowledge, the ERASE Trial is the first randomized controlled trial to examine the efficacy of HIIT in men with localized PCa on AS. As hypothesized, a supervised 12-week HIIT program significantly improved cardiorespiratory fitness. There were also significant improvements in PSA levels and velocity and functional fitness including muscular endurance and flexibility. No significant changes were found in PSA doubling time, other functional fitness outcomes, or weight and waist circumferences.

Our finding of the changes in cardiopulmonary fitness suggests an important benefit of HIIT to protect cardiovascular disease (CVD), considering approximately three times higher risk of CVD-related death compared to PCa-specific death in men with PCa on AS [2]. Moreover, higher fitness levels are associated with longer PSA doubling time in PCa patients, which suggests that HIIT may have the potential to delay PCa progression [10]. However, the magnitude of the VO_{2peak} improvement in our study did not reach our initial target of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$. A meta-analysis of exercise and cardiorespiratory fitness in cancer patients showed that, compared with usual care, aerobic exercise training significantly improved VO_{2peak} by 2.4, 1.4, and 2.5 $ml \cdot kg^{-1} \cdot min^{-1}$ before, during, and after treatments, respectively [25]. Moreover, a recent study showed that a HIIT intervention in testicular cancer survivors who completed treatment elicited a VO_{2peak} improvement of 3.7 $ml \cdot kg^{-1} \cdot min^{-1}$ compared to UC [26]. Given the high attendance (96%) and compliance (100%) rates to the HIIT program in our study, it is unclear why the magnitude of improvement in VO_{2peak} was lower compared to the previous studies. One possible explanation is the characteristics of our study participants who were very early-staged with no plan for radical treatment at the time of recruitment and were relatively fit and healthy at baseline compared to PCa patients who were undergoing or had undergone treatments [27-31].

The higher fitness levels at baseline may have resulted from one of our inclusion criteria to include those who were performing moderate-intensity exercise. In addition, our HIIT regimen with 2-minute interval might not have exerted sufficient metabolic strain and training stimulus compared to longer high-intensity exercise (e.g., 4-minute) [32], even though the greater magnitudes of improvements were observed with 2-minute HIIT protocols in cardiac patients [33, 34] as well as untrained healthy men [35]. It was unclear as we were not able to measure actual oxygen consumption during exercise and did not have interim assessments for VO_{2peak}. Future trials of HIIT in PCa patients on AS may consider excluding men who are fit at baseline or performing regular moderate-intensity exercise, and may also consider testing a HIIT protocol with longer high-intensity interval.

As hypothesized, we found a significant reduction in biochemical progression of PCa in the HIIT group compared to the UC group. Most exercise trials in PCa patients did not find notable changes in PSA levels after exercise training [27-31]. This may be because patients in these studies were undergoing androgen deprivation therapy and/or radiation therapy, which may have substantially influenced serum PSA levels, not allowing to identify the isolated effect of exercise on PCa progression. Similarly, the Prostate Cancer Novel Therapy (PANTERA) Trial [13] examined the feasibility of a year-long exercise intervention in 50 men on AS and PSA levels did not change in the exercise group, although exploratory. In contrast, a few lifestyle interventions have focused on AS settings and showed contradicting findings of PSA and prostate disease progression [36-38]. For example, the Prostate Cancer Lifestyle Trial (PCLT) in 93 PCa patients on AS found that a 1-year of diet, exercise, and stress management program yielded a reduction in PSA levels (between-group difference, -0.63 ug/L; p=0.016) [38] and there were 22% fewer men in the intervention group who proceeded to curative PCa treatments at 2-

year follow-up compared to UC [37]. In our study, we demonstrated for the first time that exercise training alone improved the biochemical progression of PCa in men on AS. Compared to the exercise program in the PANTERA Trial (i.e., 1-year, supervised plus home-based, aerobic exercise targetting 150 min/week at moderate-to-vigorous intensity), our intervention focused on high-intensity aerobic training (i.e., 85-95%) for a shorter-term (i.e., 12-week) which exerted greater physiological changes (e.g., sympathetic activation and mobilization of cytotoxic immune cells) [39, 40]. This may imply that high-intensity aerobic exercise might be necessary to produce changes in biochemical outcomes of PCa. Future research should investigate whether HIIT would benefit long-term clinical outcomes including biochemical and pathological progression of PCa.

PSA velocity and PSA doubling time are associated with PCa progression and mortality independent of PSA [41, 42]. PSA velocity>0.75 $ug \cdot L^{-1} \cdot year^{-1}$ has been used as a criterion of progression to radical treatment in AS settings [43], and the change of PSA velocity in our study of -1.3 $ug \cdot L^{-1} \cdot year^{-1}$ may be clinically meaningful. Furthermore, we found a non-significant but meaningful between-group difference in PSA doubling time of 17.9 months (p=0.10), which may further suggest a role of high-intensity aerobic exercise for delayed PCa progression consistent with previous evidence [10]. Still, it is important to note that PSA kinetics have mostly been examined in patients with advanced PCa [6] and are still under investigation for their clinical utility in disease reclassification and prognosis in the AS setting [44]. Therefore, caution is required when interpreting PSA kinetics in AS patient cohorts.

The biological mechanisms of the effects of exercise on PCa are unclear but have been suggested. One promising mechanism is the enhanced immunosurveillance after exercise training or even during a single bout of exercise can [45, 46]. Specifically, exercise can mobilize

cytotoxic natural killer cells into circulating blood and redistribute them into tumour cells assisted by norepinephrine and interleukin-6 [40], and this process appears to require endurance exercise at high-intensity [10, 45]. Exercise may also suppress PCa progression by reducing systemic inflammatory mediators [47], improving metabolic biomarkers such as IGFBP-1 [9], and increasing tumour vascularization and perfusion [48]. More research in prehabilitative clinical settings are necessary to identify key bio-physiological links between exercise and PCa in relation to PSA [49] and to explore potential tumour-related biomarkers including circulating tumour cell [50] and Ki-67 [51].

Implications of our findings include that the ERASE Trial informs larger-scale randomized controlled trials with long-term clinical outcomes including disease classification progression to radical treatments. To date, the PANTERA Trial [13] demonstrated the feasibility and acceptability of longer-term exercise training, and Galvao et al. [52] have been conducting a randomized controlled trial to examine the effect of 1-year, supervised, high-intensity, aerobic and resistance exercise training on time to initiation of curative therapy for 2-year follow-up in AS patients. Ultimately, the effectiveness of pragmatic or community-based exercise interventions that can be delivered to broader groups of PCa patients undergoing AS (e.g., home-based or telephone-based) should be investigated.

Our study has important strengths and limitations. Strengths of our study include the novel cancer setting and exercise intervention, the randomized controlled trial design, high adherence and compliance rates to the intervention, minimal loss to follow-up, and assessment of PCa-specific biomarkers. Limitations include failure to achieve our target sample size (n=52/66), potential recruitment bias (e.g., more fit and active men), unblinded outcome assessors for the primary outcome, and lack of long-term follow-up with clinical outcomes.

In conclusion, the ERASE Trial is the first randomized controlled trial to demonstrate the efficacy of HIIT for improving physical fitness and PSA levels in men with localized PCa on AS. Our findings suggest that supervised aerobic HIIT may be a promising intervention in this clinical setting. Larger-scale randomized controlled trials are warranted to determine if improvements in physical fitness and PSA levels translate into improved long-term clinical outcomes in these men such as disease progression, receipt of radical treatments, posttreatment complications, and survival.

3.6 References

1. Mahal BA, Butler S, Franco I, Spratt DE, Rebbeck TR, D'Amico AV, et al., Use of Active Surveillance or Watchful Waiting for Low-Risk Prostate Cancer and Management Trends Across Risk Groups in the United States, 2010-2015. *JAMA*, 2019. **321**(7): p. 704-6.
2. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al., 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1415-24.
3. Neal DE, Metcalfe C, Donovan JL, Lane JA, Davis M, Young GJ, et al., Ten-year Mortality, Disease Progression, and Treatment-related Side Effects in Men with Localised Prostate Cancer from the ProtecT Randomised Controlled Trial According to Treatment Received. *European Urology*, 2020. **77**(3): p. 320-30.
4. Dragomir A, Cury FL, and Aprikian AG, Active surveillance for low-risk prostate cancer compared with immediate treatment: a Canadian cost comparison. *CMAJ Open*, 2014. **2**(2): p. E60-8.
5. Keegan KA, Dall'Era MA, Durbin-Johnson B, and Evans CP, Active surveillance for prostate cancer compared with immediate treatment: an economic analysis. *Cancer*, 2012. **118**(14): p. 3512-8.
6. National Comprehensive Cancer Network (NCCN), *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer*. 2019.
7. Bourke L, Smith D, Steed L, Hooper R, Carter A, Catto J, et al., Exercise for men with prostate cancer: a systematic review and meta-analysis. *European urology*, 2016. **69**(4): p. 693-703.

8. Jones LW, Antonelli J, Masko EM, Broadwater G, Lascola CD, Fels D, et al., Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. *J Appl Physiol (1985)*, 2012. **113**(2): p. 263-72.

9. Rundqvist H, Augsten M, Stromberg A, Rullman E, Mijwel S, Kharaziha P, et al., Effect of acute exercise on prostate cancer cell growth. *PLoS One*, 2013. **8**(7): p. e67579.

10. Hvid T, Lindegaard B, Winding K, Iversen P, Brasso K, Solomon TP, et al., Effect of a 2-year home-based endurance training intervention on physiological function and PSA doubling time in prostate cancer patients. *Cancer Causes Control*, 2016. **27**(2): p. 165-74.

11. Singh F, Newton RU, Baker MK, Spry NA, Taaffe DR, Thavaseelan J, et al., Feasibility of Presurgical Exercise in Men With Prostate Cancer Undergoing Prostatectomy. *Integr Cancer Ther*, 2017. **16**(3): p. 290-9.

12. Demark-Wahnefried W, Rais-Bahrami S, Desmond RA, Gordetsky JB, Hunter GR, Yang ES, et al., Presurgical weight loss affects tumour traits and circulating biomarkers in men with prostate cancer. *Br J Cancer*, 2017. **117**(9): p. 1303-13.

13. Bourke L, Stevenson R, Turner R, Hooper R, Sasieni P, Greasley R, et al., Exercise training as a novel primary treatment for localised prostate cancer: a multi-site randomised controlled phase II study. *Sci Rep*, 2018. **8**(1): p. 8374.

14. Kang DW, Fairey AS, Boulé NG, Field CJ, and Courneya KS, Exercise duRing Active Surveillance for prostatE cancer-the ERASE trial: a study protocol of a phase II randomised controlled trial. *BMJ Open*, 2019. **9**(7): p. e026438.

15. McInnis KJ and Balady GJ, Comparison of submaximal exercise responses using the Bruce vs modified Bruce protocols. *Med Sci Sports Exerc*, 1994. **26**(1): p. 103-7.

16. Beltz NM, Gibson AL, Janot JM, Kravitz L, Mermier CM, and Dalleck LC, Graded Exercise Testing Protocols for the Determination of VO2max: Historical Perspectives, Progress, and Future Considerations. *J Sports Med (Hindawi Publ Corp)*, 2016. **2016**: p. 3968393.

17. Arlen PM, Bianco F, Dahut WL, D'Amico A, Figg WD, Freedland SJ, et al., Prostate Specific Antigen Working Group Guidelines on Prostate Specific Antigen Doubling Time. *Journal of Urology*, 2008. **179**(6): p. 2181-6.

18. Rikli RE and Jones CJ, *Senior fitness test manual*. 2013: Human Kinetics.

19. American College of Sports Medicine, *ACSM's guidelines for exercise testing and prescription*. 2013: Lippincott Williams & Wilkins.

20. Godin G and Shephard R, Godin leisure-time exercise questionnaire. *Med Sci Sports Exerc*, 1997. **29**(6): p. 36-8.

21. Borm GF, Fransen J, and Lemmens WA, A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol*, 2007. **60**(12): p. 1234-8.

22. Loprinzi PD and Kohli M. *Effect of physical activity and sedentary behavior on serum prostate-specific antigen concentrations: results from the National Health and Nutrition Examination Survey (NHANES), 2003-2006*. in *Mayo Clinic Proceedings*. 2013. Elsevier.

23. Burton AJ, Martin RM, Donovan JL, Lane JA, Davis M, Hamdy FC, et al., Associations of lifestyle factors and anthropometric measures with repeat PSA levels during active surveillance/monitoring. *Cancer Epidemiol Biomarkers Prev*, 2012. **21**(10): p. 1877-85.

24. Stofan JR, DiPietro L, Davis D, Kohl 3rd H, and Blair SN, Physical activity patterns associated with cardiorespiratory fitness and reduced mortality: the Aerobics Center Longitudinal Study. *American journal of public health*, 1998. **88**(12): p. 1807-13.

25. Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS, et al., Efficacy of Exercise Therapy on Cardiorespiratory Fitness in Patients With Cancer: A Systematic Review and Meta-Analysis. *J Clin Oncol*, 2018. **36**(22): p. 2297-305.

26. Adams SC, DeLorey DS, Davenport MH, Stickland MK, Fairey AS, North S, et al., Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: A phase 2 randomized controlled trial. *Cancer*, 2017. **123**(20): p. 4057-65.

27. Cormie P, Galvão DA, Spry N, Joseph D, Chee R, Taaffe DR, et al., Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU international*, 2015. **115**(2): p. 256-66.

28. Galvao DA, Spry N, Denham J, Taaffe DR, Cormie P, Joseph D, et al., A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. *Eur Urol*, 2014. **65**(5): p. 856-64.

29. Galvao DA, Taaffe DR, Spry N, Joseph D, and Newton RU, Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*, 2010. **28**(2): p. 340-7.

30. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al., Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*, 2009. **27**(3): p. 344-51.

31. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, et al., Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol*, 2003. **21**(9): p. 1653-9.

32. Schluter K, Schneider J, Sprave T, Wiskemann J, and Rosenberger F, Feasibility of Two High-Intensity Interval Training Protocols in Cancer Survivors. *Med Sci Sports Exerc*, 2019. **51**(12): p. 2443-50.

33. Cardozo GG, Oliveira RB, and Farinatti PT, Effects of high intensity interval versus moderate continuous training on markers of ventilatory and cardiac efficiency in coronary heart disease patients. *ScientificWorldJournal*, 2015. **2015**: p. 192479.

34. Warburton DE, McKenzie DC, Haykowsky MJ, Taylor A, Shoemaker P, Ignaszewski AP, et al., Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *Am J Cardiol*, 2005. **95**(9): p. 1080-4.

35. Nybo L, Sundstrup E, Jakobsen MD, Mohr M, Hornstrup T, Simonsen L, et al., High-intensity training versus traditional exercise interventions for promoting health. *Med Sci Sports Exerc*, 2010. **42**(10): p. 1951-8.

36. Eriksen AK, Hansen RD, Borre M, Larsen RG, Jensen JM, Overgaard K, et al., A lifestyle intervention among elderly men on active surveillance for non-aggressive prostate cancer: a randomised feasibility study with whole-grain rye and exercise. *Trials*, 2017. **18**(1): p. 20.

37. Frattaroli J, Weidner G, Dnistrian AM, Kemp C, Daubenmier JJ, Marlin RO, et al., Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology*, 2008. **72**(6): p. 1319-23.

38. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al., Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*, 2005. **174**(3): p. 1065-9; discussion 9-70.

39. Hojman P, Gehl J, Christensen JF, and Pedersen BK, Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. *Cell Metab*, 2018. **27**(1): p. 10-21.

40. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al., Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. *Cell Metab*, 2016. **23**(3): p. 554-62.

41. Carter HB, Ferrucci L, Kettermann A, Landis P, Wright EJ, Epstein JI, et al., Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst*, 2006. **98**(21): p. 1521-7.

42. Loeb S, Carter HB, Schaeffer EM, Kettermann A, Ferrucci L, and Metter EJ, Distribution of PSA velocity by total PSA levels: data from the Baltimore Longitudinal Study of Aging. *Urology*, 2011. **77**(1): p. 143-7.

43. Dall'Era MA, Konety BR, Cowan JE, Shinohara K, Stauf F, Cooperberg MR, et al., Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer*, 2008. **112**(12): p. 2664-70.

44. Vickers AJ and Brewster SF, PSA Velocity and Doubling Time in Diagnosis and Prognosis of Prostate Cancer. *British journal of medical & surgical urology*, 2012. **5**(4): p. 162-8.

45. Idorn M and Hojman P, Exercise-Dependent Regulation of NK Cells in Cancer Protection. *Trends Mol Med*, 2016. **22**(7): p. 565-77.

46. Biro PA, Thomas F, Ujvari B, and Beckmann C, Can Energetic Capacity Help Explain Why Physical Activity Reduces Cancer Risk? *Trends in cancer*, 2020.

47. Hayes BD, Brady L, Pollak M, and Finn SP, Exercise and Prostate Cancer: Evidence and Proposed Mechanisms for Disease Modification. *Cancer Epidemiol Biomarkers Prev*, 2016. **25**(9): p. 1281-8.

48. McCullough DJ, Nguyen LM, Siemann DW, and Behnke BJ, Effects of exercise training on tumor hypoxia and vascular function in the rodent preclinical orthotopic prostate cancer model. *J Appl Physiol (1985)*, 2013. **115**(12): p. 1846-54.

49. Lee K, Zhou J, Norris MK, Chow C, and Dieli-Conwright CM, Prehabilitative Exercise for the Enhancement of Physical, Psychosocial, and Biological Outcomes Among Patients Diagnosed with Cancer. *Curr Oncol Rep*, 2020. **22**(7): p. 71.

50. Neal D and Lilja H, Circulating Tumor Cell Count as an Indicator of Treatment Benefit in Advanced Prostate Cancer. *Eur Urol*, 2016. **70**(6): p. 993-4.

51. Guéritat J, Lefeuvre-Orfila L, Vincent S, Crétual A, Ravanat J-L, Gratas-Delamarche A, et al., Exercise training combined with antioxidant supplementation prevents the antiproliferative activity of their single treatment in prostate cancer through inhibition of redox adaptation. *Free Radical Biology and Medicine*, 2014. **77**: p. 95-105.

52. Galvao DA, Hayne D, Frydenberg M, Chambers SK, Taaffe DR, Spry N, et al., Can exercise delay transition to active therapy in men with low-grade prostate cancer? A multicentre randomised controlled trial. *BMJ Open*, 2018. **8**(4): p. e022331.

Table 3-1. Baseline characteristics of participants in the ERASE trial.

Variables	Overall (N=52)	HIIT (N=26)	UC (N=26)
Sociodemographic Profile			
Age (years)	63.4±7.1	63.9±7.5	62.8±6.9
Ethnicity, Caucasian	46 (88.5)	25 (96.2)	21 (80.8)
Marital status, married	37 (71.2)	17 (65.4)	20 (76.9)
Education, completed University/College	20 (38.5)	9 (34.6)	11 (42.3)
Employment status, employed	32 (62.7)	12 (48.0)	20 (76.9)
Family income, > $100,000/year	21 (40.4)	9 (34.6)	12 (46.2)
Medical Profile			
Weight (kg)	89.1±16.3	89.3±18.7	88.8±14.0
Body mass index (kg/m^2)	29.0±4.7	29.0±5.7	29.0±3.5
Waist circumference (cm)	102.3±13.4	101.4±14.4	103.3±12.6
Waist-hip ratio	0.99±0.08	0.98±0.09	1.01±0.07
Number of comorbidities			
0	9 (17.3)	4 (15.4)	5 (19.2)
1	14 (26.9)	7 (26.9)	7 (26.9)
2	16 (30.8)	8 (30.8)	8 (30.8)
≥3	13 (25.0)	7 (26.9)	6 (23.1)
Most common comorbidities			
Arthritis/arthralgia	31 (59.6)	16 (61.5)	15 (57.7)
Hypertension	16 (30.8)	8 (30.8)	8 (30.8)
Metabolic condition	9 (17.3)	4 (15.4)	5 (19.2)
Prostate Cancer Profile			
Clinical stage			
T1c	47 (90.4)	24 (92.3)	23 (88.5)
T2a	4 (7.7)	2 (7.7)	2 (7.7)
T2b	1 (1.9)	0 (0.0)	1 (3.8)
Gleason grade			
1 (3+3=6)	50 (96.2)	25 (96.2)	25 (96.2)
2 (3+4=7)	2 (3.8)	1 (3.8)	1 (3.8)
PSA (ug/L)	7.3±3.2	6.0±2.3	8.6±3.5
Prostate volume (cc)	52.9±21.5	55.6±24.8	50.3±17.6
PSA density (ug·L^{-1}·cc^{-1})	0.13±0.07	0.11±0.06	0.16±0.08
Positive cores (%)	21.6±13.0	22.9±14.2	18.3±10.5
Time on active surveillance (month)	23.0±25.8	26.7±27.0	19.4±24.4
Behavioral Profile			
Smoking			
Current smoker	1 (1.9)	1 (3.8)	0 (0.0)
Former smoker	29 (55.8)	15 (57.7)	14 (53.8)
Alcohol			
Regular drinker	6 (11.5)	3 (11.5)	3 (11.5)
Social drinker	39 (75.0)	19 (73.1)	20 (76.9)
Exercise behavior			
Vigorous aerobic exercise (min/week)	0±0	0±0	0±0
Moderate aerobic exercise (min/week)	61±99	59±74	62±120
Resistance exercise (min/week)	31±54	18±42	44±62

Data are presented as mean±standard deviation or N (%). HIIT, high-intensity interval training; UC, usual care; M, mean; SD, standard deviation; PSA, prostate-specific antigen.

Table 3-2. Effects of 12 weeks of high-intensity interval training on health-related fitness in prostate cancer patients undergoing active surveillance in the ERASE trial.

Variables	Baseline		Postintervention		Mean change		Adjusted between-group difference		
	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	*P*
Cardiopulmonary Fitness									
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)									
HIIT (n=23)	29.6	5.8	30.4	6.1	0.9	0.0 to 1.7	1.6	0.3 to 2.9	0.014
UC (n=23)	28.4	6.9	27.9	7.0	-0.5	-1.4 to 0.4			
VO_{2peak} (L/min)									
HIIT (n=23)	2.55	0.56	2.60	0.58	0.05	-0.01 to 0.12	0.12	0.00 to 0.20	0.026
UC (n=23)	2.51	0.64	2.46	0.64	-0.05	-0.13 to 0.03			
Functional Fitness									
Chair sit-stand (reps)									
HIIT (n=24)	16	5	17	5	2	0 to 3	1	0 to 3	0.15
UC (n=25)	15	4	15	4	1	0 to 2			
Arm curl (reps)									
HIIT (n=24)	17	5	19	5	2	1 to 3	3	1 to 4	0.001
UC (n=25)	18	5	18	6	0	-1 to 1			
Sit-and-reach (cm)									
HIIT (n=24)	-6.3	14.5	-3.6	17.4	2.6	-1.1 to 6.4	4.8	0.2 to 9.4	0.042
UC (n=25)	-4.4	11.5	-7.2	13.5	-2.8	-5.6 to -0.1			
Back scratch (cm)									
HIIT (n=23)	-14.7	16.0	-11.9	17.4	2.8	-0.8 to 6.5	3.7	-0.4 to 7.8	0.072
UC (n=25)	-15.3	11.3	-16.3	12.1	-0.9	-2.5 to 0.6			
8-foot up & go (sec)									
HIIT (n=24)	4.2	1.0	4.2	1.0	0.0	-0.2 to 0.2	0.6	-0.4 to 1.7	0.22
UC (n=25)	4.1	0.9	3.8	2.3	-0.4	-1.5 to 0.7			
6MWT (meter)									
HIIT (n=24)	559	65	586	71	27	12 to 41	20	-2 to 41	0.072
UC (n=25)	579	72	585	66	6	-10 to 22			
Body Weight/Size									
Body weight (kg)									
HIIT (n=24)	87.1	16.8	86.3	16.4	-0.8	-1.5 to -0.1	-0.8	-1.8 to 0.3	0.15
UC (n=25)	88.9	14.3	88.9	14.9	0.0	-0.8 to 0.7			
Waist circumference (cm)									
HIIT (n=24)	100.2	13.9	99.7	13.6	-0.4	-1.7 to 0.8	-0.7	-2.5 to 1	0.41
UC (n=25)	103.5	12.8	104.1	13.2	0.6	-0.6 to 1.8			

Between-group difference was adjusted for strength exercise behaviors and baseline value of the outcome. SD, standard deviation; CI, confidence interval; VO_{2peak}, volume of peak oxygen consumption; HIIT, high-intensity interval training; UC, usual care; 6MWT, 6-minute walk test.

Table 3-3. Effects of 12 weeks of high-intensity interval training on prostate cancer-related markers in prostate cancer patients undergoing active surveillance in the ERASE trial.

Variables	Baseline		Postintervention		Mean change		Adjusted between-group difference		
	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	*P*
PSA (ug/L)									
HIIT (n=24)	6.1	2.2	5.7	1.7	-0.4	-0.8 to 0.0	-1.1	-2.1 to 0.0	0.043
UC (n=25)	8.3	3.2	8.6	4.2	0.3	-0.7 to 1.3			
PSA doubling time (months)									
HIIT (n=23)	61.3	39.1	80.2	49.5	18.9	-1.2 to 38.9	17.9	-3.8 to 39.6	0.10
UC (n=24)	57.3	37.6	62.0	36.5	4.7	-7.0 to 16.5			
PSA velocity ($ug \cdot L^{-1} \cdot year^{-1}$)									
HIIT (n=23)	1.1	3.3	0.1	1.7	-1.0	-2.1 to 0.1	-1.3	-2.5 to -0.1	0.040
UC (n=24)	1.3	5.0	1.2	5.2	-0.1	-1.0 to 0.8			
Testosterone (nmol/L)									
HIIT (n=22)	13.5	4.6	13.9	3.9	0.4	-1.0 to 1.7	1.0	-0.7 to 2.6	0.24
UC (n=23)	12.1	3.9	12.0	3.7	-0.1	-1.2 to 1.0			

Between-group difference was adjusted for aerobic and resistance exercise behaviors and baseline value of the outcome. SD, standard deviation; CI, confidence interval; PSA, prostate-specific antigen.

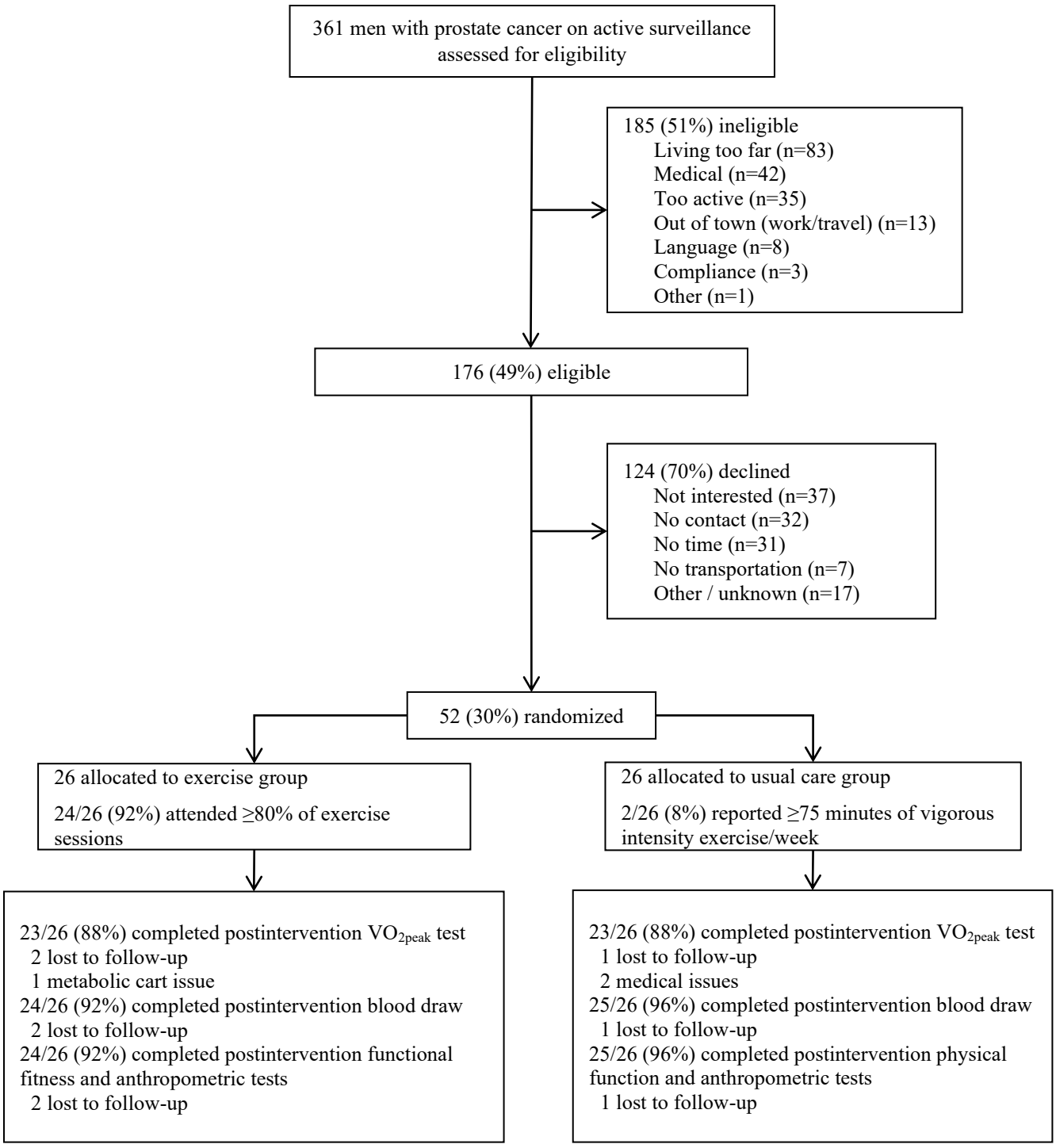


Figure 3-1. CONSORT diagram of the ERASE Trial.

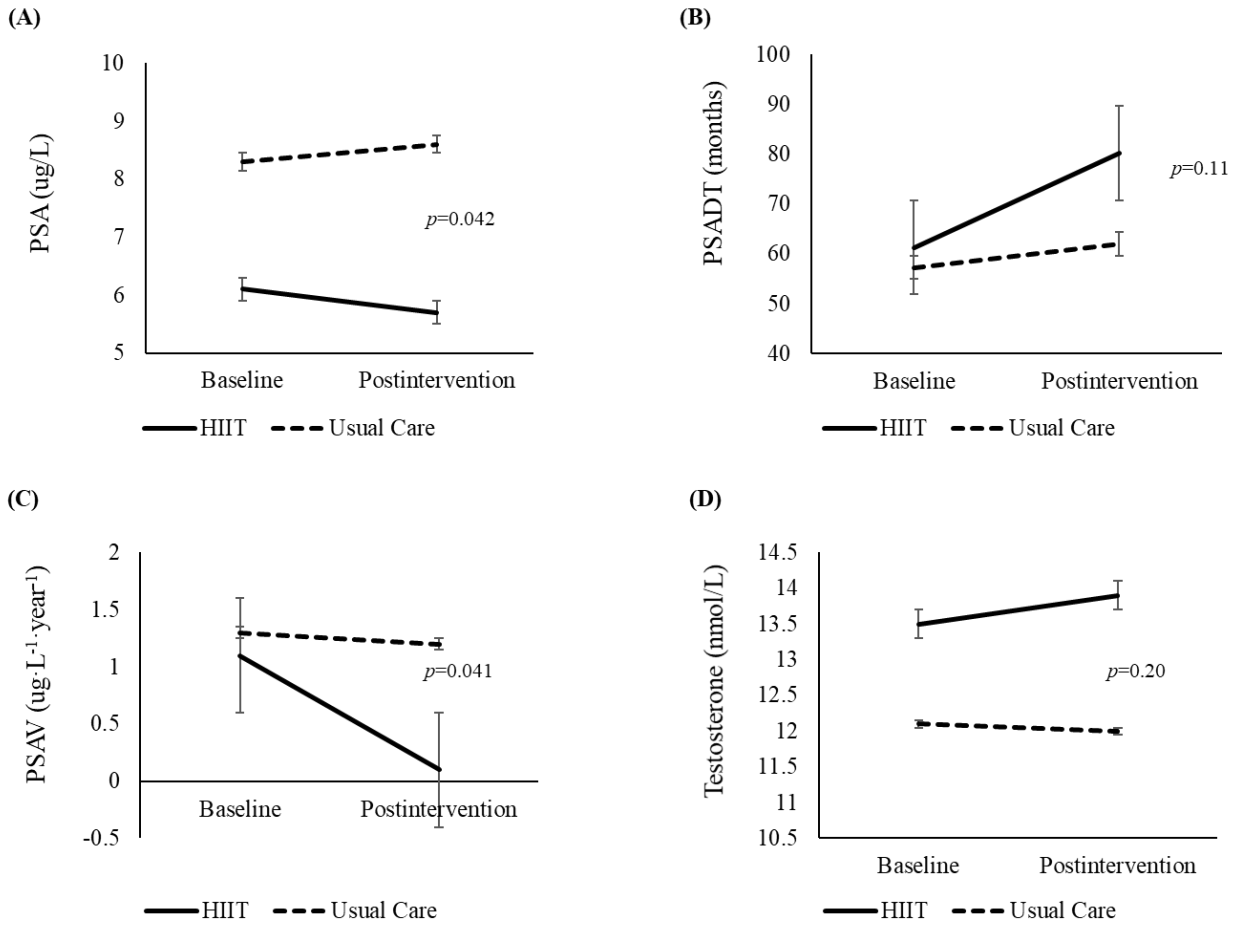


Figure 3-2. Effects of exercise on prostate cancer-specific antigen, doubling time, and velocity in prostate cancer patients on active surveillance in the ERASE trial. *p*-values indicate between-group difference at postintervention using analysis of covariance adjusting for resistance exercise behaviours and baseline value of the outcome. Error bars indicate standard error. HIIT, high-intensity interval training; PSA, prostate-specific antigen; PSADT, PSA doubling time; PSAV, PSA velocity.

CHAPTER 4 – PAPER 3 (Biomarkers)

Effects of high-intensity interval training on cardiometabolic and inflammatory biomarkers in prostate cancer patients undergoing active surveillance: A randomized controlled trial

4.1 Abstract

Purpose: To report the effects of a 12-week aerobic high-intensity interval training (HIIT) program on cardiometabolic and inflammatory biomarkers in prostate cancer (PCa) patients on active surveillance (AS) from the ERASE Trial.

Methods: A total of 52 men diagnosed with PCa on AS were recruited. Participants were randomized to either exercise (HIIT; n=26) or usual care (UC; n=26) group. The HIIT intervention consisted of progressive, supervised, aerobic HIIT at an intensity of 85 to 95% VO_{2peak} for 28 to 40 minutes per session performed three times/week for 12 weeks. Fasting blood was collected at baseline and postintervention. Cardiometabolic biomarkers included fasting glucose and circulating lipid profiles, and inflammatory cytokines included interleukin (IL)-axis, c-reactive protein (CRP), and tumour necrosis factor-alpha (TNF-α). Analysis of covariance was used to determine significant adjusted between-group mean differences.

Results: In the ERASE Trial, participants were aged 63.4±7.1 years and 40% were obese. Blood data were obtained from 49/52 (94%) participants. Participants in the HIIT group attended 96% of the planned exercise sessions. Compared to UC, HIIT significantly reduced total cholesterol (between-group difference, -0.40 mmol/L; 95% confidence interval[CI], -0.70 to -0.10; *p*=0.011), non-high-density lipoprotein-c (between-group difference, -0.35 mmol/L; 95% CI, -0.60 to -0.11; *p*=0.006), IL-1β (between-group difference, -0.050 pg/ml; 95% CI, -0.085 to -0.015; *p*=0.006), IL-4 (between-group difference, 0.013 pg/ml; 95% CI, -0.024 to -0.003; *p*=0.017), and IL-12p70 (between-group difference, -0.119 pg/ml; 95% CI, -0.207 to -0.032; *p*=0.009). No significant differences were found in other cytokines including IL-6, c-reactive protein, and tumour necrosis factor-α.

Conclusions: HIIT significantly reduced several lipid markers and inflammatory cytokines, and an overall trend of improvement in these outcomes was observed. HIIT may provide cardioprotective benefits and reduce PCa-related systemic inflammation in men with PCa on AS.

4.2 Introduction

One in seven men in Canada is diagnosed with prostate cancer over their lifetime, with approximately 23,000 new cases each year [1]. Low-to-moderate grade prostate cancers are often indolent and managed by active surveillance, where patients can avoid immediate invasive treatment and are regularly monitored for any sign of disease progression. About one in three men on active surveillance eventually experience disease progression and undergo invasive treatment, however, the most common cause of death among early-stage prostate cancer patients is cardiovascular disease (CVD), followed by second cancers and other cardiometabolic diseases [2].

Increased levels of cardiometabolic and inflammatory biomarkers such as glucose, lipids, interleukin (IL)-6, and c-reactive protein (CRP), are linked to CVD, metabolic disease and can be improved by physical activity [3]. Recent meta-analyses of randomized controlled trials support the positive effects of exercise on cardiometabolic and inflammatory biomarkers in cancer patients [4, 5][6, 7]. Most of these studies, however, have focused on breast cancer patients [5-7] or prostate cancer patients during androgen deprivation therapy (ADT) [4]. Only one study has been conducted in prostate cancer patients undergoing active surveillance and it reported some preliminary effects of exercise on blood outcomes [8]. In the Exercise During Active Surveillance for Prostate Cancer (ERASE) trial [9], we previously reported the benefits of high-intensity interval training (HIIT) on cardiopulmonary fitness and prostate-specific antigen in prostate cancer patients on active surveillance. Here, we report the changes in cardiometabolic and inflammatory outcomes in the ERASE trial. We hypothesized that, compared to usual care (UC), HIIT would improve blood outcomes related to cardiometabolic disease and systemic inflammation in prostate cancer patients undergoing active surveillance.

4.3 Methods

Study Design and Population

Detailed study methods of the ERASE Trial have been published elsewhere [9]. The ERASE Trial was a randomized controlled trial examining the effects of a 12-week aerobic HIIT in prostate cancer patients on active surveillance. The trial was registered to clinicaltrial.gov (NCT03203460) and approved by the Health Research Ethics Board of Alberta – Cancer Committee (HREBA.CC-17-0248). All participants provided written consent for study participation and blood banking. Participants were recruited from the Kaye Edmonton Clinic in Edmonton, Alberta, Canada. Eligibility criteria included 18 years of age or above, having been diagnosis with prostate cancer and undergoing active surveillance, no plan for any curative treatment at the time of recruitment, not having contraindications for or being medically cleared for performing cardiopulmonary fitness test and high-intensity aerobic training such as uncontrolled hypertension, and no participation in any structured vigorous-intensity exercise. Once patients agreed to participate in the study, baseline blood draw and fitness assessments were completed and participants were randomized either to HIIT or UC.

Exercise Intervention

Details of the study interventions have been described elsewhere [9]. In brief, the HIIT group was given a supervised, thrice-weekly, aerobic HIIT program for 12-weeks. Each HIIT session comprised 2 minutes of high-intensity exercise (workload corresponding to 85-95% VO_{2peak}) followed by 2 minutes of light-intensity exercise recovery (workload corresponding to 40% VO_{2peak}), with progression from 5 to 8 intervals resulting in 28 minutes to 40 minutes of exercise (including warm-up and cool-down for 5 minutes each). Participants in the UC group were asked not to begin any structured high-intensity exercise during the intervention period (12

weeks). They were then offered a 4-week HIIT program at your facility and a 12-week community-based exercise program.

Blood Outcome Measures

Fasting (≥ 12 hours) blood samples were collected at the Kaye Edmonton Clinic Laboratory Services. Serum blood was drawn in the 6.0mL red top tube, clotted for 30-60 minutes, and spin for 20 minutes at 2860 rpm. 0.75mL of serum was transferred to each of the four cryovials provided. Fasting glucose, HbA1c, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non-HDL-C were analyzed on fresh serum at the central processing laboratory and the results were available through medical records. Two additional 6.0ml EDTA were collected for inflammatory cytokines and sent to the biochemistry lab in the Li Ka Shing Centre for Health Research Innovation at the University of Alberta. Plasma & buffy coat samples were spin for 10 minutes at 2860 rpm within one hour of collection and 1.0mL of plasma was transferred to a secondary tube to each of the eight cryovials. Samples were frozen and stored at -70°C until the completion of blood collection from all participants at baseline and postintervention in order to assay the samples at the same time using paired assays plated in random order to minimize measurement errors. Inflammatory cytokines including IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF)-α, and high sensitive (hs)-CRP were analyzed using a sandwich immunoassay (Meso Scale Discovery, Gaithersburg, MD, USA). Duplicate testing was performed with coefficients of variation for all samples < 10%. The lab technicians were blinded to the treatments and appropriate standard and reference samples were included in each assay.

Statistical Analyses

The planned sample size was 66 (33 participants per group) to detect a between-group mean difference of 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ with an SD of 5.6 mL/kg/min on our primary outcome of VO_{2peak} with 80% power using a two-tailed $\alpha < 0.05$. This power was also sufficient for detecting standardized effects sizes of approximately d=0.5 for the blood outcomes of the study. Missing values were not replaced due to low missing data (<5%). Extreme outliers that were greater than three times the interquartile range were removed [10]. Data normality was explored using skewness and kurtosis. Due to the approximately normal distribution of the data and equal and sufficient sample size in each group, analysis of covariance was performed to determine significant between-group mean differences at postintervention adjusting for baseline value of the outcome. SPSS version 26 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

4.4 Results

Participant flow in the ERASE trial has been reported elsewhere (**Chapter 3**; **Figure 3-1**). In brief, a total of 52 PCa patients undergoing active surveillance were randomized either to the HIIT (n=26) or UC (n=26) group. Postintervention biomarkers data were obtained in 24/26 (92%) participants in the HIIT group and 25/26 (96%) participants in the UC group. The HIIT group attended 96% of planned exercise sessions with 100% compliance to the exercise protocol.

Demographic, behavioural, and medical profiles of the ERASE participants have been described elsewhere (**Chapter 3**; **Table 3-1**). Briefly, the mean age was 63.4±7.1, the mean body mass index was 29.0±4.7, 83% had one or more comorbidities with 60% arthritis/arthralgia, 31% hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg, 17% dyslipidemia (LDL-c>6.0 mmol/L), and 4% diabetes (fasting glucose≥7.0 mmol/L or

HbA1c≥6.5%). 12% were regular drinkers, 2% were current smokers, and the average time spent in moderate-intensity exercise was 61±99 minutes per week. 90% were T1c stage PCa, 96% Gleason grade of 6, the mean PSA level was 7.3±3.2, and the mean time since starting active surveillance was 1.9±2.2 years. We have previously reported that the HIIT group showed significant improvement in VO_{2peak} by 1.6 $ml \cdot kg^{-1} \cdot min^{-1}$ (p=0.014) and PSA by -1.1 $ug \cdot L^{-1}$ (p=0.042) compared to the UC group.

The changes in cardiometabolic biomarkers from baseline to postintervention are presented in **Table 4-1**. There were significant between-group differences in TC (adjusted between-group mean difference, -0.40 mmol/L; 95% confidence interval[CI], -0.70 to -0.10; p=0.011) and non-HDL-C (adjusted between-group mean difference, -0.35 mmol/L; 95% CI, -0.60 to -0.11; p=0.006). No significant between-group differences were found in fasting glucose, HbA1c, TG, HDL-C, and LDL-C. The changes of inflammatory cytokines are presented in **Table 4-2**. Significant between-group differences were found in IL-1β (adjusted between-group mean difference, -0.050 pg/ml; 95% CI, -0.085 to -0.015; p=0.006), IL-4 (adjusted between-group mean difference, -0.013 pg/ml; 95% CI, -0.024 to -0.003; p=0.017), and IL-12p70 (adjusted between-group mean difference, -0.119 pg/ml; 95% CI, -0.207 to -0.032; p=0.009). No significant between-group differences were found in IL-2, IL-6, IL-8, IL-10, IL-13, IFN-γ, TNF-α, and hs-CRP.

4.5 Discussion

We have previously reported from the ERASE trial that 12-weeks of aerobic HIIT yielded improvements in cardiopulmonary and functional fitness and a decrease in biochemical progression of prostate cancer [**Chapter 3**; **Table 3-2**, **Table 3-3**]. In this report, we presented

that HIIT resulted in significant reductions in TC and non-HDL-C. HIIT also reduced inflammatory cytokines such as IL-1β, IL-4, and IL-12p70, which may have positive implications related to PCa.

The probability of CVD-related death in men diagnosed with early-staged prostate cancer is as threefold higher compared to prostate cancer-specific death [11]. The impact of exercise on lipid parameters, as strong predictors of CVD [12], has been studied in prostate cancer patients [4, 8], and most studies were done during ADT, where a meta-analysis did not find significant improvements on any lipid parameters [4]. Similarly, one preliminary study focusing on prostate cancer patients undergoing active surveillance (Prostate Cancer Novel Therapy; PANTERA) did not observe a trend favouring their physical activity intervention [8]. The discrepancies between these results and our findings of significant improvements in TC and non-HDL-C may be attributed to the mode and dose of exercise regimen [13]. Given that changes in systemic cholesterol levels are more susceptible to higher dose (intensity or duration) aerobic exercise [13], resistance training-focused exercise programs during ADT or a low-dose community-based physical activity program during active surveillance in previous studies might not have exerted notable changes in blood lipids compared to our HIIT intervention. This is consistent to recent randomized controlled trials reporting significant improvements in serum cholesterol levels after HIIT in breast [14] and testicular [15] cancer survivors. Therefore, our findings suggest that HIIT may play a role in lowering risks of CVD by improving blood lipids in prostate cancer patients during active surveillance. Still, more research should further establish which exercise mode and dose would be optimal in this cancer population.

HIIT also exerted reductions in proinflammatory cytokines, which were comparable with a recent meta-analysis [16], reporting that most proinflammatory cytokines tend to decrease with

exercise training in cancer patients (pooled standardized mean difference, -0.253; p=0.001). Consistent findings have been observed for a few tumour-related cytokines, such as IL-6, CRP, or TNF-α, which have been widely studied mostly in breast cancer patients [5, 6, 16]. In our study, significant reductions were found in IL-1β, IL-4, and IL-12p70, and only IL-1β was included in a meta-analysis [16] and its reduction with exercise did not reach statistical significance. Given the roles of IL-1β [17] and IL-4 [18] in androgen-dependent prostate cancer cell line (LNCaP) signalling, our findings may provide evidence for the link between exercise and reduction in the proliferation of LNCaP [19]. Furthermore, preoperative IL-12p70 is associated with biochemical recurrence of prostate cancer [20], and the change of IL-12p70 in our study might have played as a mediator of the lengthened prostate-specific antigen doubling time after 2-year of endurance exercise training in a previous study [21]. To date, IL-6 and TNF-α have been identified as important cytokines attributing to the effects of exercise on suppression of prostate tumour progression [22, 23], however, the roles of exercise on other pro- or anti-inflammatory cytokines in prostate cancer should be further examined in both preclinical and clinical settings

The importance of chronic inflammatory cytokines in prostate cancer progression has been addressed in active surveillance settings [24]. For example, increased IL-6, one of the most studied cytokines in prostate cancer, is associated with prostate cancer progression and higher mortality [25, 26]. A number of exercise randomized controlled trials have investigated the effects of exercise training on inflammatory cytokines in cancer survivors [16]. Khosravi et al. conducted a meta-analysis and showed that exercise yielded a significant reduction in CRP and TNF-α as well as non-significant decreases in IL-6, IL-8, INF-γ, and IL-1β [16], which suggests that larger sample sizes may be needed. The mechanisms have been suggested that exercise

training lowers chronic systemic inflammation, which may modulate the inflammation-immune axis and increase immune infiltration in tumours, resulting in suppression in cancer progression [27]. However, it appears that the effects of exercise on inflammatory cytokines can be highly heterogeneous depending on cancer type, treatment status, and exercise mode and intensity [16]. Future studies should determine the impacts and mechanisms of different modalities of exercise on systemic changes of inflammatory markers in cancer survivors.

In our study, there were no changes of metabolic biomarkers in both the HIIT and UC groups. Previous exercise trials found improvements in fasting blood glucose in men with prostate cancer undergoing ADT [4]. However, consistent with our study findings, the PANTERA study in active surveillance patients did not find an improvement in HbA1c [8]. It is unclear why our exercise intervention did not improve glucose regulation as metabolic markers [28], however, it may be partially due to the study population with generally normal glucose levels, where exercise may not be expected to further improve such metabolic outcomes.

Strengths of our study include randomized controlled trial design in a novel cancer population, high-intensity exercise intervention that might have exerted greater physiological responses, high study follow-up and intervention adherence rates, and complex set of inflammatory cytokines. Limitations include statistical analyses on multiple inflammatory outcomes that might have increased a chance finding and potential recruitment bias (selection bias).

In conclusion, the ERASE Trials examined for the first time the effects of HIIT on cardiometabolic and inflammatory biomarkers in men with prostate cancer patients on active surveillance. Our findings of lower values for some lipid parameters and inflammatory cytokines suggest that a 12-week high-intensity aerobic exercise training may improve cardiovascular

health and systemic inflammation that might lower the risks of CVD and prostate cancer progression. Larger trials need to further determine the longer-term effects of exercise on disease-related biomarkers and clinical events in prostate cancer patients undergoing active surveillance.

4.6 References

1. Canadian Cancer Society, *Canadian Cancer Statistics 2019*. 2019.
2. Riihimäki M, Thomsen H, Brandt A, Sundquist J, and Hemminki K, What do prostate cancer patients die of? *The oncologist*, 2011. **16**(2): p. 175.
3. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, and Alfano CM, Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *Journal of the National Cancer Institute*, 2012. **104**(11): p. 815-40.
4. Bigaran A, Zopf E, Gardner J, La Gerche A, Murphy DG, Howden EJ, et al., The effect of exercise training on cardiometabolic health in men with prostate cancer receiving androgen deprivation therapy: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*, 2020.
5. Meneses-Echávez JF, Correa-Bautista JE, González-Jiménez E, Schmidt Río-Valle J, Elkins MR, Lobelo F, et al., The Effect of Exercise Training on Mediators of Inflammation in Breast Cancer Survivors: A Systematic Review with Meta-analysis. *Cancer Epidemiology Biomarkers & Prevention*, 2016. **25**(7): p. 1009-17.
6. Kang DW, Lee J, Suh SH, Ligibel J, Courneya KS, and Jeon JY, Effects of Exercise on Insulin, IGF Axis, Adipocytokines, and Inflammatory Markers in Breast Cancer Survivors: A Systematic Review and Meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 2017. **26**(3): p. 355-65.
7. Wang Y, Jin B, Paxton RJ, Yang W, Wang X, Jiao Y, et al., The effects of exercise on insulin, glucose, IGF-axis and CRP in cancer survivors: Meta-analysis and meta-regression of randomised controlled trials. *Eur J Cancer Care (Engl)*, 2020. **29**(1): p. e13186.

8. Bourke L, Stevenson R, Turner R, Hooper R, Sasieni P, Greasley R, et al., Exercise training as a novel primary treatment for localised prostate cancer: a multi-site randomised controlled phase II study. *Sci Rep*, 2018. **8**(1): p. 8374.

9. Kang DW, Fairey AS, Boulé NG, Field CJ, and Courneya KS, Exercise duRing Active Surveillance for prostatE cancer-the ERASE trial: a study protocol of a phase II randomised controlled trial. *BMJ Open*, 2019. **9**(7): p. e026438.

10. Ghasemi A and Zahediasl S, Normality tests for statistical analysis: a guide for non-statisticians. *International journal of endocrinology and metabolism*, 2012. **10**(2): p. 486.

11. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al., 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1415-24.

12. Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, et al., Lipid-related markers and cardiovascular disease prediction. *Jama*, 2012. **307**(23): p. 2499-506.

13. Mann S, Beedie C, and Jimenez A, Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. *Sports medicine (Auckland, N.Z.)*, 2014. **44**(2): p. 211-21.

14. Lee K, Tripathy D, Demark-Wahnefried W, Courneya KS, Sami N, Bernstein L, et al., Effect of Aerobic and Resistance Exercise Intervention on Cardiovascular Disease Risk in Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. *JAMA Oncol*, 2019. **5**(5): p. 710-4.

15. Adams SC, DeLorey DS, Davenport MH, Stickland MK, Fairey AS, North S, et al., Effects of high-intensity aerobic interval training on cardiovascular disease risk in

testicular cancer survivors: A phase 2 randomized controlled trial. *Cancer*, 2017. **123**(20): p. 4057-65.

16. Khosravi N, Stoner L, Farajivafa V, and Hanson ED, Exercise training, circulating cytokine levels and immune function in cancer survivors: A meta-analysis. *Brain, Behavior, and Immunity*, 2019. **81**: p. 92-104.
17. Bent R, Moll L, Grabbe S, and Bros M, Interleukin-1 beta—a friend or foe in malignancies? *International journal of molecular sciences*, 2018. **19**(8): p. 2155.
18. UEDA T, SADAR MD, SUZUKI H, AKAKURA K, SAKAMOTO S, SHIMBO M, et al., Interleukin-4 in patients with prostate cancer. *Anticancer research*, 2005. **25**(6C): p. 4595-8.
19. Rundqvist H, Augsten M, Stromberg A, Rullman E, Mijwel S, Kharaziha P, et al., Effect of acute exercise on prostate cancer cell growth. *PLoS One*, 2013. **8**(7): p. e67579.
20. Kazzazi A, Momtahen S, Bruhn A, Hemani M, Ramaswamy K, and Djavan B, New findings in localized and advanced prostate cancer: AUA 2011 review. *Can J Urol*, 2011. **18**(3): p. 568398.
21. Hvid T, Lindegaard B, Winding K, Iversen P, Brasso K, Solomon TP, et al., Effect of a 2-year home-based endurance training intervention on physiological function and PSA doubling time in prostate cancer patients. *Cancer Causes Control*, 2016. **27**(2): p. 165-74.
22. Hayes BD, Brady L, Pollak M, and Finn SP, Exercise and Prostate Cancer: Evidence and Proposed Mechanisms for Disease Modification. *Cancer Epidemiol Biomarkers Prev*, 2016. **25**(9): p. 1281-8.

23. Jones LW, Antonelli J, Masko EM, Broadwater G, Lascola CD, Fels D, et al., Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. *J Appl Physiol (1985)*, 2012. **113**(2): p. 263-72.

24. Hayashi T, Fujita K, Matsushita M, and Nonomura N, Main Inflammatory Cells and Potentials of Anti-Inflammatory Agents in Prostate Cancer. *Cancers (Basel)*, 2019. **11**(8).

25. Twillie DA, Eisenberger MA, Carducci MA, Hseih W-S, Kim WY, and Simons JW, Interleukin-6: a candidate mediator of human prostate cancer morbidity. *Urology*, 1995. **45**(3): p. 542-9.

26. George DJ, Halabi S, Shepard TF, Sanford B, Vogelzang NJ, Small EJ, et al., The prognostic significance of plasma interleukin-6 levels in patients with metastatic hormone-refractory prostate cancer: results from cancer and leukemia group B 9480. *Clinical Cancer Research*, 2005. **11**(5): p. 1815-20.

27. Koelwyn GJ, Wennerberg E, Demaria S, and Jones LW, Exercise in Regulation of Inflammation-Immune Axis Function in Cancer Initiation and Progression. *Oncology (Williston Park)*, 2015. **29**(12): p. 908-20, 22.

28. Norton L, Norton K, and Lewis N, Exercise training improves fasting glucose control. *Open access journal of sports medicine*, 2012. **3**: p. 209.

Table 4-1. Effects of a 12-week high-intensity interval training on cardiometabolic biomarkers in prostate cancer patients undergoing active surveillance in the ERASE trial.

Variables	Baseline	Postintervention	Change from baseline	*p*
	Mean (SD)	Mean (SD)	Mean (95% CI)	
Fasting glucose (mmol/L)				
HIIT (n=23)	5.6 (0.6)	5.7 (0.5)	0.0 (-0.2 to 0.2)	0.88
UC (n=24)	5.5 (0.7)	5.6 (0.6)		
HbA1c (%)				
HIIT (n=23)	5.7 (0.5)	5.7 (0.4)	0.0 (-0.1 to 0.1)	0.77
UC (n=24)	5.7 (0.3)	5.8 (0.4)		
Triglycerides (mmol/L)				
HIIT (n=24)	1.69 (0.91)	1.55 (0.73)	-0.10 (-0.37 to 0.17)	0.46
UC (n=25)	1.46 (0.72)	1.48 (0.79)		
Total cholesterol (mmol/L)				
HIIT (n=24)	4.83 (0.85)	4.69 (0.85)	-0.40 (-0.70 to -0.10)	0.011
UC (n=24)	4.64 (0.83)	4.90 (1.12)		
HDL-C (mmol/L)				
HIIT (n=24)	1.22 (0.23)	1.21 (0.25)	0.03 (-0.05 to 0.11)	0.50
UC (n=24)	1.23 (0.24)	1.19 (0.20)		
LDL-C (mmol/L)				
HIIT (n=24)	2.79 (0.76)	2.77 (0.75)	-0.17 (-0.40 to 0.06)	0.14
UC (n=23)	2.70 (0.74)	2.84 (0.92)		
Non-HDL-C (mmol/L)				
HIIT (n=24)	3.60 (0.94)	3.47 (0.94)	-0.35 (-0.60 to -0.11)	0.006
UC (n=24)	3.40 (0.78)	3.62 (0.99)		

Analysis of covariance were conducted to determine between-group differences at postintervention adjusting for baseline value of the outcome. CI, confidence interval; HIIT, high-intensity interval training; UC, usual care; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 4-2. Effects of a 12-week high-intensity interval training on inflammatory cytokines in prostate cancer patients undergoing active surveillance in the ERASE trial.

Variables	Baseline	Postintervention	Adjusted between-group mean difference	*p*
	Mean (SD)	Mean (SD)	Mean (95% CI)	
IL-1β (pg/ml)				
HIIT (n=23)	0.075 (0.070)	0.056 (0.038)	-0.050 (-0.085 to -0.015)	0.006
UC (n=25)	0.092 (0.063)	0.109 (0.073)		
IL-2 (pg/ml)				
HIIT (n=21)	0.521 (0.293)	0.404 (0.151)	-0.116 (-0.269 to 0.037)	0.13
UC (n=25)	0.892 (0.675)	0.848 (0.705)		
IL-4 (pg/ml)				
HIIT (n=22)	0.065 (0.053)	0.052 (0.012)	-0.013 (-0.024 to -0.003)	0.017
UC (n=25)	0.061 (0.021)	0.065 (0.023)		
IL-6 (pg/ml)				
HIIT (n=23)	1.117 (0.581)	0.978 (0.458)	-0.077 (-0.298 to 0.144)	0.49
UC (n=25)	0.962 (0.540)	0.966 (0.508)		
IL-8 (pg/ml)				
HIIT (n=23)	2.249 (0.791)	2.441 (1.046)	0.112 (-0.393 to 0.617)	0.66
UC (n=25)	2.096 (0.653)	2.203 (1.005)		
IL-10 (pg/ml)				
HIIT (n=23)	0.460 (0.226)	0.387 (0.174)	-0.054 (-0.127 to 0.019)	0.15
UC (n=25)	0.408 (0.215)	0.409 (0.190)		
IL-12p70 (pg/ml)				
HIIT (n=22)	0.304 (0.184)	0.250 (0.113)	-0.119 (-0.207 to -0.032)	0.009
UC (n=25)	0.491 (0.413)	0.527 (0.410)		
IL-13 (pg/ml)				
HIIT (n=22)	2.010 (0.956)	1.785 (0.728)	-0.372 (-0.909 to 0.166)	0.17
UC (n=25)	3.321 (2.328)	3.369 (2.489)		
IFN-γ (pg/ml)				
HIIT (n=21)	6.582 (3.347)	6.719 (3.291)	-0.382 (-1.801 to 1.037)	0.59
UC (n=25)	5.978 (2.884)	6.608 (3.489)		
TNF-α (pg/ml)				
HIIT (n=24)	0.967 (0.432)	0.981 (0.469)	0.002 (-0.098 to 0.102)	0.97
UC (n=25)	0.870 (0.319)	0.883 (0.337)		
hs-CRP (mg/L)				
HIIT (n=20)	2.9 (2.4)	2.2 (2.1)	-0.3 (-1.2 to 0.7)	0.58
UC (n=25)	2.1 (1.8)	2.1 (1.7)		

Analysis of covariance were conducted to determine between-group differences at postintervention adjusting for baseline value of the outcome. CI, confidence interval; HIIT, high-intensity interval training; UC, usual care; IL, interleukin ; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha; hs-CRP, high-sensitive c-reactive protein.

CHAPTER 5 – PAPER 4 (Patient-reported Outcomes)

Effects of high-intensity interval training on anxiety, fear of cancer progression, and quality of life in prostate cancer patients on active surveillance: A randomized controlled trial

5.1 Abstract

Purpose: To examine the effects of a 12-week exercise program on patient-reported outcomes in prostate cancer (PCa) patients on active surveillance (AS).

Methods: 52 PCa patients undergoing AS were randomized to high-intensity interval training (HIIT; n=26) or usual care (UC; n=26). The HIIT group performed a 12-week, thrice-weekly, supervised, aerobic HIIT intervention. Patient-reported outcomes were assessed at baseline and postintervention (12-weeks), including PCa-specific anxiety (Memorial Anxiety Scale for Prostate Cancer; MAX-PC), fear of cancer progression (Fear of Cancer Recurrence Inventory; FCRI), PCa-related symptoms (Expanded Prostate Cancer Index Composite-26; EPIC-26), cancer-related quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; EORTC QLQ–C30), and generic psychosocial outcomes (e.g., fatigue, stress, and self-esteem). Analysis of covariance was used to compare between-group differences.

Results: 50/52 (96%) participants completed patient-reported outcome assessments at 12-weeks and adherence to the HIIT program was 96%. Compared to UC, HIIT significantly reduced total PCa-specific anxiety (adjusted between-group mean difference, -2.7; 95% confidence interval[CI], -5.0 to -0.4; p=0.024; d=0.28) and fear of recurrence (adjusted between-group mean difference, -2.0; 95% CI, -3.5 to -0.4; p=0.013; d=0.67) in MAX-PC; hormonal dysfunction (p=0.005) in EPIC-26; and perceived stress (p=0.037), fatigue (p=0.029), and self-esteem (p=0.007).

Conclusions: A 12-week supervised HIIT program reduced PCa-specific anxiety, fear of cancer progression, hormone symptoms, stress, and fatigue, and increased self-esteem in men with PCa

on AS. Larger trials are warranted to determine the longer-term effects of exercise on patient-reported outcomes and whether such effects influence willingness to continue on AS.

5.2 Introduction

Prostate cancer (PCa) treatments have side effects, including sexual and urinary dysfunction, fatigue, and reduced quality of life (QOL) [1, 2]. Active surveillance (AS) allows men with low-to-moderate grade PCa to avoid immediate treatments and their side effects until PCa becomes clinically significant [3]. Due to these advantages, the number of PCa patients being offered AS continues to increase [4]. Unfortunately, PCa patients on AS have a higher chance of disease progression and metastasis, and approximately 55% will have radical treatment within ten years [5]. Increased anxiety and fear of cancer progression are concerns among PCa patients on AS [6, 7] that are associated with poor QOL [8] and may even prompt these men to opt for radical treatments in the absence of clinical PCa progression [9]. Interventions to reduce anxiety and fear of cancer progression in these men may improve QOL and reduce the chances of them opting for medically unnecessary radical treatments.

Exercise has been shown to significantly improve anxiety and QOL in PCa patients during and after radical treatments [10-13]; however, no study to date has examined the role of exercise in managing the psychosocial distress that arises in the AS setting. Moreover, no study to date has examined the effects of exercise on fear of cancer recurrence/progression in any cancer patient group. We conducted the Exercise During Active Surveillance for Prostate Cancer (ERASE) Trial to examine the effects of exercise in PCa patients on AS [14]. We previously reported that a 12 week, high-intensity interval training (HIIT) program significantly improved cardiovascular fitness and reduced prostate-specific antigen (PSA) levels and velocity (**Chapter 3**; **Table 3-3**). Here, we report the effects of the exercise intervention on patient-reported outcomes, including PCa-specific anxiety, fear of cancer progression, PCa symptoms, QOL, and

psychosocial outcomes. We hypothesized that HIIT would improve each of these patient-reported outcomes in PCa patients undergoing AS compared to usual care (UC).

5.3 Methods

Study Design

Study protocol and methods of the ERASE Trial have been reported elsewhere [14]. In brief, this single-centre, two-armed randomized controlled trial compared a 12-week HIIT program with UC on changes in physical fitness, cancer-related biomarkers, and patient-reported outcomes. The study was conducted at the University of Alberta and the Kaye Edmonton Clinic in Edmonton, Alberta, Canada and approved by the Health Research Ethics Board of Alberta – Cancer Committee (HREBA.CC-17-0248). Written informed consent was obtained from all participants. The trial was registered with clinicaltrial.gov (NCT03203460).

Participants, Recruitment, and Randomization

Eligible participants were (1) ≥18 years old, (2) diagnosed with PCa and currently undergoing AS as the primary management strategy, (3) having no plans for radical treatment at the time of recruitment, (4) medically cleared for study participation, (5) not performing any vigorous-intensity exercise, and (6) English-speaking. PCa patients on AS identified through medical records were referred to the study coordinator by their urologists during their checkup visits. Patients who agreed to participate in the study were scheduled for baseline assessments and, upon the completion of the assessments, were randomized to the HIIT or UC group. The randomization sequence was produced using a computer-generated program with a 1:1 ratio and random blocks of 4 or 6. It was concealed from study staff involved in recruitment and baseline assessment. Due to the nature of the exercise intervention, participants and interventionists were

not blinded to group assignment when completing the patient-reported outcomes at postintervention.

Intervention

The exercise intervention has been described in detail elsewhere [14]. In brief, the HIIT group was provided with a 12-week supervised aerobic HIIT program three times per week on a treadmill. Each exercise session consisted of a warm-up at 60% of VO_{2peak} for 5 minutes, high-intensity walking or jogging at 85 to 95% VO_{2peak} for 2 minutes followed by active recovery at 40% of VO_{2peak} for 2 minutes, and alternating high-intensity intervals and recovery for 5 to 8 times. Exercise intensity and the number of intervals during each session were progressed over the intervention period. After each session, participants conducted a cool-down at 30% of VO_{2peak} for 5 minutes and stretching for lower body muscles for 5 minutes. The UC group was asked to maintain their baseline exercise levels during the intervention period. Upon the completion of the postintervention assessments at 12-weeks, participants in the UC group were offered a 4-week HIIT program at our facility and given information about a 12-week community-based exercise program.

Patient-Reported Outcome Measures

Patient-reported outcome measures in the ERASE Trial have been described elsewhere [14]. In brief, patient-reported outcomes were assessed by questionnaire at baseline and postintervention (12 weeks). Participants were asked to complete the questionnaire within one week of the assessment dates. PCa-specific anxiety was assessed by the Memorial Anxiety Scale for Prostate Cancer (MAX-PC) [15]. MAX-PC consists of 18 items with three subscales assessing PCa anxiety, PSA anxiety, and fear of recurrence. The total and subscale score ranges are 0-54, 0-33, 0-9, and 0-25. Scores above 27, 16, 4, and 6, respectively, are considered a high

degree of anxiety [16]. Fear of cancer progression was assessed using the 9-item Fear of Cancer Recurrence Inventory (FCRI) short-form [17] and the 8-item Cancer Worry Scale (CWS) [18]. The FCRI short-form and CWS were modified to adapt to the AS context by replacing "recurrence" or "development" with "progression".

PCa symptoms were assessed using the Expanded Prostate Cancer Index Composite-26 (EPIC-26) [19]. EPIC-26 comprises 5 PCa-related symptom scales, including urinary symptoms (e.g., urinary incontinence and irritative/obstructive), bowel symptoms (e.g., abdominal bloating and diarrhea), sexual symptoms (e.g., erectile dysfunction and lack of sexual desire) and hormonal (testosterone-related) symptoms (e.g., lack of energy and loss of weight). Values range from 0 to 100, and higher values indicate better symptoms. Minimally important difference (MID) was determined as 8, 6, 5, 11, and 5 for each of the five subscales above, respectively [20]. Cancer-related QOL was assessed by the European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire Core 30-item (EORTC QLQ – C30) [21]. The EORTC QLQ-C30 consists of 15 subscales, including global health status/QOL, five functional scales (physical, role, emotional, cognitive, and social), eight symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), and financial difficulties. All values range from 0 to 100, and higher values indicate better QOL for global health status and functional scales, and worse symptoms for symptom scales and financial difficulties. MID was determined as between-group mean difference of 10 [22, 23].

General anxiety, depression, fatigue, and stress were assessed using the 10-item Spielberger State-Trait Anxiety Inventory (STAI) [24], the 10-item Center for Epidemiologic Studies-Depression Scale (CES-D) [25], the 13-item Functional Assessment of Cancer Therapy-Fatigue (FACT-F) Scale [26], and the 14-item Perceived Stress Scale (PSS) [27], respectively.

Self-esteem was measured using the 10-item Rosenberg Self-Esteem Scale (RSES) [28]. Higher values indicate worse psychosocial status for anxiety, depression, and stress; and better psychosocial status for fatigue and self-esteem. For fatigue, MID of 3 was used [29]. Baseline demographic and behavioural information was obtained using a self-reported questionnaire, including age, ethnicity, education, marital status, income, employment status, smoking, alcohol consumption, and exercise behaviour.

Statistical Analyses

With the targeted sample size of 66 (33 participants per group) and the adjustment for the baseline values of the outcome and selected covariates, our study would provide 80% power using a two-tailed alpha <0.05 to detect a between-group mean difference of 3.5 mL/kg/min with an SD of 5.6 mL/kg/min on our primary outcome of VO_{2peak}. This power was also sufficient for detecting the standardized effects sizes of approximately d=0.5. MID was used for interpretation of the results when appropriate. We performed analyses of covariance to compare the between-group differences at postintervention after adjustment for covariates. Covariates included baseline values of the outcome and other demographic variables that were unbalanced at baseline between the two groups. All study participants who had baseline and postintervention data were included for statistical analysis, and scores were calculated based on all available data. No adjustment was made for multiple testing, and no missing data strategy was used because of very low missing data (<5%). SPSS version 26 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

5.4 Results

Flow of study participants has been reported elsewhere (**Chapter 3**; **Figure 3-1**). In brief, 52 PCa patients on AS were enrolled in the study and 26 participants were randomized to each group. Attendance at the HIIT program was 96% with 100% compliance to the HIIT protocol. At postintervention, patient-reported outcome data were available from 50/52 (96%) participants (25 from each group).

Participants' demographic, behavioural, and medical information at baseline have been reported elsewhere (**Chapter 3**; **Table 3-1**). Briefly, participants were on average 63.4±7.1 years of age, 89% Caucasian, 71% married, 39% completed university/college, 63% employed, 40% were obese, 83% had comorbidities, 58% were current or former smokers, 90% had T1c stage PCa, 96% were Gleason grade of 6, the average PSA level was 7.3±3.2, and the average time since starting AS was 23±26 months. Marital status and employment status were not balanced between groups (HIIT: 65% vs. UC: 77% [p=0.034] and HIIT: 48% vs. UC: 77% [p=0.026], respectively) and were adjusted for in the analyses. As previously reported (**Chapter 3**; **Table 3-2**, **Table 3-3**), HIIT significantly improved VO_{2peak} by 1.6 ml/kg/min (p=0.014) and reduced PSA by -1.1 (p=0.042) compared to UC.

Patient-Reported Outcomes

The effects of HIIT on PCa-specific anxiety and fear of cancer progression are reported in **Table 5-1**. For MAX-PC, participants in the HIIT group showed a significant reduction in total PCa-specific anxiety (adjusted between-group mean difference, -2.7; 95% CI, -5.0 to -0.4; p=0.024; d=0.28) and fear of recurrence (adjusted between-group mean difference, -2.0; 95% CI, -3.5 to -0.4; p=0.013; d=0.67) compared to the UC group (**Figure 5-1**). No significant differences were observed for FCRI and CWS.

The effects of HIIT on PCa symptoms are presented in **Table 5-2**. HIIT showed a significant improvement in self-reported hormonal symptom (less symptom) compared to UC (adjusted between-group mean difference, 6.0; 95% CI, 2.0 to 10.1; p=0.005; d=0.55). No significant between-group differences were found in urinary, bowel, or sexual quality of life.

The effects of HIIT on cancer-related QOL are shown in **Table 5-3**. Compared to the UC group, the HIIT group showed a borderline significant increase in global health status/QOL (adjusted between-group mean difference, 6.8; 95% CI, -0.4 to 13.9; p=0.062; d=0.49) and emotional functioning (adjusted between-group mean difference, 5.6; 95% CI, -1.1 to 12.2; p=0.098; d=0.30). There were no significant between-group differences in functional and symptom scales and financial difficulties.

The effects of HIIT on general psychosocial outcomes are shown in **Table 5-4**. HIIT significantly reduced perceived stress (adjusted between-group mean difference, -3.7; 95% CI, -7.2 to -0.2; p=0.037; d=0.57) and fatigue (adjusted between-group mean difference, 3.2; 95% CI, 0.4 to 6.1; p=0.029; d=0.48) and increased self-esteem (adjusted between-group mean difference, 3.1; 95% CI, 0.9 to 5.3; p=0.007; d=0.69). No significant differences were observed in general anxiety and depression.

5.5 Discussion

In our study, a 12-week aerobic HIIT program that improved cardiopulmonary fitness and PSA in PCa patients on AS (**Chapter 3**; **Table 3-2**, **Table 3-3**) also elicited positive changes in important patient-reported outcomes. Specifically, HIIT reduced PCa-specific anxiety (total score and fear of recurrence), hormonal dysfunction, and general psychosocial outcomes (stress, fatigue, and self-esteem) compared to the UC group. For cancer-related QOL, global health

status/QOL showed a trend to increase. To our knowledge, our findings demonstrate for the first time the efficacy of exercise for improving patient-reported outcomes in men with PCa undergoing AS.

Perhaps most important clinically, we found a significant decrease in overall PCa-specific anxiety after 12-weeks of HIIT exercise compared to UC with a small-moderate effect size. Anxiety has been identified as one of the major psychological distresses among PCa patients on AS [30-32] and is associated with a 5% to 13% increase in AS discontinuation [31, 33-35]. Strong evidence supports that aerobic exercise reduces anxiety in cancer survivors [36] both during [37] and after [38] treatments. More specifically for PCa patients, a meta-analysis showed that exercise produced a marginally significant reduction in anxiety [39]. Most PCa patients included in these studies, however, had completed or were receiving radical treatment [40, 41]. Our study is the first to suggest that exercise may manage the anxiety that arises from being on AS for PCa. If so, it is also possible that exercise may help some PCa patients remain on AS longer.

Interestingly, the decrease in overall PCa-specific anxiety was largely attributable to the decrease in fear of cancer recurrence (progression). We observed a large standardized effect size and there was a notable reduction in the number of participants in the HIIT group who had clinically high fear of cancer progression from 9/25 (36%) to 3/25 (12%) compared to the UC group which showed no change from 10/25 (40%). Fear of cancer progression is a common concern among cancer patients, as approximately 50% of cancer survivors experience moderate to severe fear of cancer progression [42]. In PCa patients, fear of cancer progression is a significant problem associated with reduced QOL [43] and, especially in AS settings, fear of cancer progression appears to influence treatment decisions [9]. The potential benefit of exercise

on fear of cancer progression in cancer survivors has been proposed previously [42], however, no data have been reported. Our study is the first to suggest that exercise may help manage fear of cancer progression in PCa patients on AS.

The effects of exercise on overall PCa-specific anxiety in our study, however, did not seem to extend to PSA- or PCa-related anxiety. For PSA-related anxiety, one possible explanation is the very low level at baseline that likely resulted in a floor effect. For PCa-related anxiety, one plausible explanation is that the questions comprising the PCa-related anxiety subscale in the MAX-PC focus on patients' past conceptualization of their PCa, whereas the fear of recurrence subscale focuses on the future influence of PCa [15]. Moreover, exercise did not significantly change fear of cancer progression measured by the FCRI and the CWS. This may be due to the differences in the target population for each questionnaire. FCRI and CWS assess general fear of cancer progression whereas the MAX-PC assesses PCa-specific fear of cancer progression. Nevertheless, future studies are needed to investigate the sensitivity and specificity of fear of cancer progression questionnaires in the context of AS.

In terms of PCa-specific symptoms, hormonal symptoms were better by a MID of 5.0 [20] in the HIIT group compared to the UC group (p=0.005). Culos-Reed et al. [44] investigated the effects of 16-week home-based aerobic and resistant training in PCa patients on androgen deprivation therapy (ADT), and hormonal symptoms showed a trend favouring the exercise group but it was not statistically significant compared to UC. It is interesting that our study found a large effect on hormonal symptoms, which are more relevant to PCa patients undergoing hormonal treatments (i.e., ADT) and may not be pertinent to AS settings. The reasons are unclear especially given that HIIT did not change testosterone levels (**Chapter 3**; **Table 3-3**); however, participants in the HIIT group might have experienced better perceived hormone-related

symptoms, such as lack of energy, feeling depressed, or change in body weight. Future studies are needed to identify specific hormone-related patient-reported outcomes that may be distinct in AS patients and whether they can be improved by exercise.

HIIT also yielded improvements in several general psychosocial outcomes, including stress, fatigue, and self-esteem. The importance of stress management during AS and the necessity of improving coping skills have been noted [45]. Our finding of reduced stress, however, is in contrast to previous studies reporting that both low-dose exercise [46] and HIIT [47] did not change perceived stress during and after cancer treatment. These data suggest that exercise may manage stress in the AS setting but not in the treatment or recovery settings. Moreover, we also found that HIIT significantly lessened fatigue which is a well-established benefit of exercise in the oncology setting [37, 38] and is consistent with a recent study of HIIT in testicular cancer survivors [47]. Although PCa patients on AS have less fatigue compared to PCa patients who undergo radical treatments [48], our finding suggests that exercise could still reduce fatigue levels in AS patients. Finally, HIIT also showed a large effect in improving self-esteem. This finding is consistent with previous studies that showed a moderate to large increase in self-esteem after exercise training in the oncology setting [37, 38, 47]. A unique aspect regarding self-esteem in AS settings is that high self-efficacy or self-esteem seems to play a key role in their treatment decision-making process and is associated with higher decisional satisfaction and QOL [49, 50]. Therefore, our finding may imply that better self-esteem through HIIT may help men on AS more actively engage in the decision-making process towards radical treatment and improve the overall satisfaction of their decisions and overall QOL.

HIIT also exerted a borderline significant but potentially meaningful increase in global health status/QOL. Strong evidence supports the benefits of exercise on cancer-related QOL

during and after cancer treatment [37, 38, 51, 52]; however, only one study has focused on AS settings [53], reporting the preliminary efficacy of a 1-year physical activity intervention on QOL. In our study, it is notable that the potential exercise effects were found in overall QOL with no changes in physical functions or symptoms. This finding is comparable to the Prostate Cancer Lifestyle Trial reporting non-significant change in QOL and physical function after a lifestyle intervention (exercise, diet, and stress management) in AS patients and these outcomes remained high across all assessment timepoints [54]. It is understandable that AS patients do not experience cancer-related or treatment-induced symptoms [1], where exercise may have had a potential ceiling or floor effect. In the AS setting, the marginally significant increase in overall QOL in our study suggests that HIIT may further elicit better cancer-related QOL without addressing physical functions and symptoms. Although not significant, the largest effect of exercise on the patient functioning subscales was for the emotional functioning subscale. These data suggest a largely psychosocial effect of exercise in the AS setting as opposed to improvements in physical functioning. Future research should investigate whether HIIT could provide long-term effects in psychosocial or functional QOL that may improve overall QOL in AS patients.

Overall strengths and limitations of the ERASE Trial have been discussed elsewhere (**Chapter 3**). The ERASE Trial was the first randomized controlled trial to examine the efficacy of exercise in men with PCa on AS. We achieved a high adherence to exercise (96%), an excellent follow-up (96%) of patient-reported outcomes, and we assessed a comprehensive set of important patient-reported outcomes in the AS setting. Limitations include the modest sample size, the likely recruitment bias (self-selection), the lack of long-term follow-up data, and the potential self-reporting bias.

In conclusion, the ERASE Trial demonstrated the benefits of a 12-week supervised HIIT program in managing PCa-specific anxiety and fear of cancer progression, hormonal dysfunction, stress, fatigue, and self-esteem. Cancer-related global health status/QOL also showed a borderline significant improvement. Our findings may have clinical implications for a subgroup of AS patients who opt for radical treatment to manage their anxiety, fear of cancer progression, or general psychosocial distress. Larger trials are warranted to further establish the longer-term effects of exercise on patient-reported outcomes and its potential impact on AS continuation.

5.6 References

1. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al., Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1425-37.
2. Chen RC, Basak R, Meyer A, and et al., Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. *JAMA*, 2017. **317**(11): p. 1141-50.
3. Parker C, Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol*, 2004. **5**(2): p. 101-6.
4. Cooperberg MR and Carroll PR, Trends in Management for Patients With Localized Prostate Cancer, 1990-2013. *JAMA*, 2015. **314**(1): p. 80-2.
5. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al., 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1415-24.
6. Wallace M, Uncertainty and quality of life of older men who undergo watchful waiting for prostate cancer. *Oncology nursing forum*, 2002. **30**(2): p. 303-9.
7. Matthew AG, Raz O, Currie KL, Louis AS, Jiang H, Davidson T, et al., Psychological distress and lifestyle disruption in low-risk prostate cancer patients: Comparison between active surveillance and radical prostatectomy. *J Psychosoc Oncol*, 2018. **36**(2): p. 159-74.
8. Parker PA, Davis JW, Latini DM, Baum G, Wang X, Ward JF, et al., Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with

favourable-risk prostate cancer undergoing active surveillance. *BJU Int*, 2016. **117**(3): p. 469-77.

9. Latini DM, Hart SL, Knight SJ, Cowan JE, Ross PL, Duchane J, et al., The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. *J Urol*, 2007. **178**(3 Pt 1): p. 826-31; discussion 31-2.

10. Cormie P, Galvão DA, Spry N, Joseph D, Chee R, Taaffe DR, et al., Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU international*, 2015. **115**(2): p. 256-66.

11. Galvao DA, Taaffe DR, Spry N, Joseph D, and Newton RU, Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*, 2010. **28**(2): p. 340-7.

12. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, et al., Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol*, 2003. **21**(9): p. 1653-9.

13. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al., Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*, 2009. **27**(3): p. 344-51.

14. Kang DW, Fairey AS, Boulé NG, Field CJ, and Courneya KS, Exercise duRing Active Surveillance for prostatE cancer-the ERASE trial: a study protocol of a phase II randomised controlled trial. *BMJ Open*, 2019. **9**(7): p. e026438.

15. Roth AJ, Rosenfeld B, Kornblith AB, Gibson C, Scher HI, Curley-Smart T, et al., The memorial anxiety scale for prostate cancer: validation of a new scale to measure anxiety in men with with prostate cancer. *Cancer*, 2003. **97**(11): p. 2910-8.

16. Roth A, Nelson CJ, Rosenfeld B, Warshowski A, O'Shea N, Scher H, et al., Assessing anxiety in men with prostate cancer: further data on the reliability and validity of the Memorial Anxiety Scale for Prostate Cancer (MAX-PC). *Psychosomatics*, 2006. **47**(4): p. 340-7.

17. Simard S and Savard J, Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. *Support Care Cancer*, 2009. **17**(3): p. 241-51.

18. Custers JA, van den Berg SW, van Laarhoven HW, Bleiker EM, Gielissen MF, and Prins JB, The Cancer Worry Scale: detecting fear of recurrence in breast cancer survivors. *Cancer Nurs*, 2014. **37**(1): p. E44-50.

19. Szymanski KM, Wei JT, Dunn RL, and Sanda MG, Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology*, 2010. **76**(5): p. 1245-50.

20. Skolarus TA, Dunn RL, Sanda MG, Chang P, Greenfield TK, Litwin MS, et al., Minimally important difference for the Expanded Prostate Cancer Index Composite Short Form. *Urology*, 2015. **85**(1): p. 101-5.

21. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al., The European-Organization-for-Research-and-Treatment-of-Cancer Qlq-C30 - a Quality-of-

Life Instrument for Use in International Clinical-Trials in Oncology. *Journal of the National Cancer Institute*, 1993. **85**(5): p. 365-76.

22. Osoba D, Rodrigues G, Myles J, Zee B, and Pater J, Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*, 1998. **16**(1): p. 139-44.
23. Cocks K, King MT, Velikova G, Fayers PM, and Brown JM, Quality, interpretation and presentation of European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 data in randomised controlled trials. *Eur J Cancer*, 2008. **44**(13): p. 1793-8.
24. Spielberger CD, *State-Trait anxiety inventory*. 2010: Wiley Online Library.
25. Lewinsohn PM, Seeley JR, Roberts RE, and Allen NB, Center for epidemiologic studies depression scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychology and Aging*, 1997. **12**(2): p. 277-87.
26. Yellen SB, Cella DF, Webster K, Blendowski C, and Kaplan E, Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*, 1997. **13**(2): p. 63-74.
27. Cohen S, Kamarck T, and Mermelstein R, A global measure of perceived stress. *J Health Soc Behav*, 1983. **24**(4): p. 385-96.
28. Rosenberg M, Rosenberg self-esteem scale (RSE). *Acceptance and commitment therapy. Measures package*, 1965. **61**: p. 52.
29. Cella D, Eton DT, Lai JS, Peterman AH, and Merkel DE, Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage*, 2002. **24**(6): p. 547-61.

30. Wallace M, Uncertainty and quality of life of older men who undergo watchful waiting for prostate cancer. *Oncol Nurs Forum*, 2003. **30**(2): p. 303-9.

31. Klotz L, Active surveillance, quality of life, and cancer-related anxiety. *Eur Urol*, 2013. **64**(1): p. 37-9.

32. Kinsella N, Stattin P, Cahill D, Brown C, Bill-Axelson A, Bratt O, et al., Factors Influencing Men's Choice of and Adherence to Active Surveillance for Low-risk Prostate Cancer: A Mixed-method Systematic Review. *Eur Urol*, 2018. **74**(3): p. 261-80.

33. Bul M, Zhu X, Rannikko A, Staerman F, Valdagni R, Pickles T, et al., Radical prostatectomy for low-risk prostate cancer following initial active surveillance: results from a prospective observational study. *Eur Urol*, 2012. **62**(2): p. 195-200.

34. Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR, et al., Active surveillance for prostate cancer: a systematic review of the literature. *Eur Urol*, 2012. **62**(6): p. 976-83.

35. van den Bergh RC, Essink-Bot M-L, Roobol MJ, Schröder FH, Bangma CH, and Steyerberg EW, Do anxiety and distress increase during active surveillance for low risk prostate cancer? *The Journal of urology*, 2010. **183**(5): p. 1786-91.

36. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al., Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc*, 2019. **51**(11): p. 2375-90.

37. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, and Topaloglu O, Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev*, 2012. **2012**(8): p. Cd008465.

38. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC, et al., Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev*, 2012. **2012**(8): p. Cd007566.

39. Vashistha V, Singh B, Kaur S, Prokop LJ, and Kaushik D, The Effects of Exercise on Fatigue, Quality of Life, and Psychological Function for Men with Prostate Cancer: Systematic Review and Meta-analyses. *Eur Urol Focus*, 2016. **2**(3): p. 284-95.

40. Cormie P, Galvão DA, Spry N, Joseph D, Chee R, Taaffe DR, et al., Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU International*, 2015. **115**(2): p. 256-66.

41. Campo RA, Agarwal N, LaStayo PC, O'Connor K, Pappas L, Boucher KM, et al., Levels of fatigue and distress in senior prostate cancer survivors enrolled in a 12-week randomized controlled trial of Qigong. *Journal of Cancer Survivorship*, 2014. **8**(1): p. 60-9.

42. Dinkel A and Herschbach P, *Fear of progression in cancer patients and survivors*, in *Psycho-Oncology*. 2018, Springer. p. 13-33.

43. van de Wal M, van Oort I, Schouten J, Thewes B, Gielissen M, and Prins J, Fear of cancer recurrence in prostate cancer survivors. *Acta Oncol*, 2016. **55**(7): p. 821-7.

44. Culos-Reed SN, Robinson JW, Lau H, Stephenson L, Keats M, Norris S, et al., Physical activity for men receiving androgen deprivation therapy for prostate cancer: benefits from a 16-week intervention. *Supportive Care in Cancer*, 2010. **18**(5): p. 591-9.

45. Yanez B, Bustillo NE, Antoni MH, Lechner SC, Dahn J, Kava B, et al., The importance of perceived stress management skills for patients with prostate cancer in active surveillance. *Journal of behavioral medicine*, 2015. **38**(2): p. 214-23.

46. Cadmus LA, Salovey P, Yu H, Chung G, Kasl S, and Irwin ML, Exercise and quality of life during and after treatment for breast cancer: results of two randomized controlled trials. *Psychooncology*, 2009. **18**(4): p. 343-52.

47. Adams SC, DeLorey DS, Davenport MH, Fairey AS, North S, and Courneya KS, Effects of high-intensity interval training on fatigue and quality of life in testicular cancer survivors. *Br J Cancer*, 2018. **118**(10): p. 1313-21.

48. Barocas DA, Alvarez J, Resnick MJ, Koyama T, Hoffman KE, Tyson MD, et al., Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. *JAMA*, 2017. **317**(11): p. 1126-40.

49. Goh AC, Kowalkowski MA, Bailey DE, Jr., Kazer MW, Knight SJ, and Latini DM, Perception of cancer and inconsistency in medical information are associated with decisional conflict: a pilot study of men with prostate cancer who undergo active surveillance. *BJU Int*, 2012. **110**(2 Pt 2): p. E50-6.

50. Menichetti J, Valdagni R, and Bellardita L, Quality of life in active surveillance and the associations with decision-making—a literature review. *Translational andrology and urology*, 2018. **7**(1): p. 160.

51. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al., Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. *Cancer Treat Rev*, 2017. **52**: p. 91-104.

52. Sweegers MG, Altenburg TM, Chinapaw MJ, Kalter J, Verdonck-de Leeuw IM, Courneya KS, et al., Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med*, 2018. **52**(8): p. 505-13.

53. Bourke L, Stevenson R, Turner R, Hooper R, Sasieni P, Greasley R, et al., Exercise training as a novel primary treatment for localised prostate cancer: a multi-site randomised controlled phase II study. *Sci Rep*, 2018. **8**(1): p. 8374.

54. Daubenmier JJ, Weidner G, Marlin R, Crutchfield L, Dunn-Emke S, Chi C, et al., Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance. *Urology*, 2006. **67**(1): p. 125-30.

Table 5-1. Effects of 12-week high-intensity interval training on anxiety and fear of cancer progression in prostate cancer patients undergoing active surveillance in the ERASE trial.

Variables (range)	Baseline		Postintervention		Mean change		Adjusted between-group difference [a]			
	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	*p*	*d*
MAX-PC										
Total score (0-54)										
HIIT (n=24)	10.6	9.4	7.7	7.4	-2.9	-4.5 to -1.2	-2.7	-5.0 to -0.4	0.024	-0.28
UC (n=25)	11.7	9.4	11.2	9.2	-0.5	-2.2 to 1.1				
Prostate cancer anxiety (0-33)										
HIIT (n=25)	6.0	6.9	4.7	5.5	-1.4	-2.9 to 0.1	-0.6	-2.4 to 1.2	0.52	-0.09
UC (n=25)	6.9	7.2	6.1	7.0	-0.8	-1.9 to 0.3				
PSA anxiety (0-9)										
HIIT (n=25)	0.4	1.3	0.5	1.0	0.1	-0.1 to 0.4	0.0	-0.4 to 0.3	0.87	0.02
UC (n=25)	0.2	1.0	0.4	1.0	0.1	-0.2 to 0.4				
Fear of recurrence (0-12)										
HIIT (n=25)	4.2	3.3	2.6	2.1	-1.6	-2.7 to -0.5	-2.0	-3.5 to -0.4	0.013	-0.67
UC (n=25)	4.6	2.6	4.7	3.2	0.2	-1.1 to 1.4				
FCRI (0-36)										
HIIT (n=25)	11.9	6.9	11.0	5.7	-0.9	-2.4 to 0.6	0.6	-1.4 to 2.6	0.55	0.09
UC (n=25)	13.5	5.9	11.6	5.4	-1.9	-3.3 to -0.5				
CWS (8-32)										
HIIT (n=25)	12.5	3.4	12.1	2.5	-0.4	-1.3 to 0.6	0.3	-0.9 to 1.5	0.58	0.11
UC (n=25)	13.3	2.2	12.5	2.8	-0.8	-1.6 to -0.1				

A higher value indicates worse anxiety or fear/worry. Between-group difference at postintervention was analyzed using analysis of covariance adjusting for marital status, employment status, and baseline value of the outcome. SD, standard deviation; CI, confidence interval; MAX-PC, Memorial Anxiety Scale for Prostate Cancer; HIIT, high-intensity interval training; UC, usual care; PSA, prostate specific antigen; FCRI, Fear of Cancer Recurrence Inventory; CWS, Cancer Worry Scale.

Table 5-2. Effects of 12-week high-intensity interval training on prostate cancer-specific symptoms in prostate cancer patients undergoing active surveillance in the ERASE trial.

Variables	Baseline		Postintervention		Mean change		Adjusted between-group difference			
	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	*p*	*d*
Urinary incontinence										
HIIT (n=25)	91.3	12.0	90.8	13.8	-0.5	-5.3 to 4.3	0.5	-7.0 to 6.0	0.88	0.04
UC (n=25)	93.1	11.0	91.5	12.1	-1.6	-5.6 to 2.5				
Urinary irritative/obstructive										
HIIT (n=25)	86.9	11.3	86.6	10.0	-0.3	-4.1 to 3.4	-2.4	-6.7 to 1.8	0.26	-0.20
UC (n=25)	86.3	13.0	89.0	10.4	2.8	-0.1 to 5.6				
Bowel										
HIIT (n=25)	97.2	4.1	95.2	7.3	-2.0	-4.3 to 0.3	0.7	-3.3 to 4.7	0.73	0.13
UC (n=25)	95.6	6.3	92.9	11.3	-2.7	-5.8 to 0.4				
Sexual										
HIIT (n=24)	67.9	23.4	70.6	23.5	2.8	-4.0 to 9.6	3.1	-6.0 to 12.2	0.49	0.12
UC (n=22)	57.0	30.1	58.7	29.8	1.7	-2.5 to 5.9				
Hormonal										
HIIT (n=25)	88.8	14.0	95.6	5.1	6.8	1.9 to 11.7	6.0	2.0 to 10.1	0.005	0.55
UC (n=24)	93.5	6.5	92.3	8.5	-1.2	-4.8 to 2.4				

Values range 0-100. A higher value indicates a better symptom. Between-group difference at postintervention was analyzed using analysis of covariance adjusting for marital status, employment status, and baseline value of the outcome. SD, standard deviation; CI, confidence interval; HIIT, high-intensity interval training; UC, usual care.

Table 5-3. Effects of 12-week high-intensity interval training on cancer-related quality of life in prostate cancer patients undergoing active surveillance in the ERASE trial.

Variables	Baseline		Postintervention		Mean change		Adjusted between-group difference			
	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	*p*	*d*
Global Health Status/QOL										
HIIT (n=25)	76.7	13.4	80.7	13.5	4.0	-1.7 to 9.7	6.8	-0.4 to 13.9	0.062	0.49
UC (n=25)	74.7	14.9	74.3	16.7	-0.3	-5.2 to 4.6				
Functional Scales										
Physical functioning										
HIIT (n=25)	94.9	8.5	96.3	6.4	1.3	-2.1 to 4.8	1.2	-2.7 to 5.0	0.55	0.17
UC (n=25)	96.8	4.8	96.3	7.2	-0.5	-3.0 to 2.0				
Role functioning										
HIIT (n=25)	94.0	12.6	94.7	13.4	0.7	-6.1 to 7.4	0.5	-6.9 to 7.8	0.90	0.04
UC (n=25)	95.3	11.3	94.7	11.5	-0.7	-6.8 to 5.4				
Emotional functioning										
HIIT (n=25)	83.3	22.4	90.3	10.9	7.0	0.1 to 13.9	5.6	-1.1 to 12.2	0.098	0.30
UC (n=25)	82.0	14.2	84.7	14.6	2.7	-3.4 to 8.7				
Cognitive functioning										
HIIT (n=25)	84.7	19.8	92.0	11.9	7.3	1.3 to 13.3	1.2	-4.4 to 6.9	0.66	0.07
UC (n=25)	86.7	13.6	92.0	9.8	5.3	-0.2 to 10.9				
Social functioning										
HIIT (n=25)	92.7	12.8	95.3	10.2	2.7	-2.5 to 7.8	-1.0	-7.5 to 5.6	0.77	-0.08
UC (n=25)	94.0	10.6	96.7	11.8	2.7	-2.5 to 7.8				
Symptom Scales										
Fatigue										
HIIT (n=25)	20.4	15.6	14.2	12.6	-6.2	-12.3 to -0.1	-5.6	-13.2 to 2.0	0.14	-0.38
UC (n=25)	13.8	13.7	16.9	13.3	3.1	-4.2 to 10.4				
Nausea and vomiting										
HIIT (n=25)	2.0	5.5	2.7	6.2	0.7	-2.5 to 3.8	1.9	-1.0 to 4.9	0.20	0.43
UC (n=25)	0.7	3.3	0.7	3.3	0.0	0.0				
Pain										
HIIT (n=25)	20.0	18.0	15.3	14.4	-4.7	-13.7 to 4.3	1.3	-7.8 to 10.4	0.78	0.08
UC (n=25)	13.3	15.2	10.7	15.1	-2.7	-9.2 to 3.8				
Dyspnea										
HIIT (n=24)	13.9	16.8	11.1	16.1	-2.8	-9.9 to 4.3	-0.4	-8.9 to 8.1	0.92	-0.03
UC (n=25)	8.0	17.4	8.0	14.5	0.0	-5.6 to 5.6				
Insomnia										
HIIT (n=25)	29.3	22.2	24.0	24.6	-5.3	-13.9 to 3.3	-5.4	-19.8 to 9.0	0.46	-0.26
UC (n=25)	21.3	19.0	22.7	28.4	1.3	-8.8 to 11.4				
Appetite loss										
HIIT (n=25)	6.7	13.6	5.3	12.5	-1.3	-6.2 to 3.5	-3.0	-9.4 to 3.5	0.36	-0.28
UC (n=25)	1.3	6.7	4.0	11.1	2.7	-1.1 to 6.5				
Constipation										
HIIT (n=25)	2.7	9.2	1.3	6.7	-1.3	-4.1 to 1.4	-4.5	-11.1 to 2.1	0.17	-0.70
UC (n=25)	0.0	0.0	2.7	13.3	2.7	-2.8 to 8.2				
Diarrhea										
HIIT (n=25)	8.0	14.5	13.3	25.5	5.3	-4.1 to 14.8	1.5	-9.4 to 12.3	0.79	0.11
UC (n=25)	5.3	12.5	10.7	18.6	5.3	0.2 to 10.5				
Financial Difficulties										
HIIT (n=25)	4.0	11.1	1.3	6.7	-2.7	-6.5 to 1.1	-0.7	-3.3 to 2.0	0.61	-0.05
UC (n=25)	2.7	13.3	1.3	6.7	-1.3	-4.1 to 1.4				

Values range 0-100. A higher value indicates better quality of life for global health status/QOL and functional scales and worse symptoms for symptom scales. Cancer-related quality of life was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ C30). Between-group difference at postintervention was analyzed using analysis of covariance adjusting for marital status, employment status, and baseline value of the outcome. SD, standard deviation; CI, confidence interval; QOL, quality of life; HIIT, high-intensity interval training; UC, usual care.

Table 5-4. Effects of 12-week high-intensity interval training on general psychosocial outcomes in prostate cancer patients undergoing active surveillance in the ERASE trial.

Variables (range)	Baseline		Postintervention		Mean change		Adjusted between-group difference			
	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	*p*	*d*
Anxiety (10-40)										
HIIT (n=25)	17.7	6.3	14.7	3.5	-3.0	-5.8 to -0.2	-1.0	-3.4 to 1.3	0.37	-0.19
UC (n=25)	16.4	4.9	15.1	4.3	-1.3	-2.8 to 0.1				
Depression (0-30)										
HIIT (n=25)	8.2	3.9	3.3	2.2	-4.9	-6.4 to -3.4	-0.7	-2.5 to 1.2	0.48	-0.19
UC (n=25)	7.4	3.2	3.6	3.8	-3.8	-5.3 to -2.3				
Stress (0-56)										
HIIT (n=25)	16.1	8.8	12.8	6.5	-3.3	-6.7 to 0.0	-3.7	-7.2 to -0.2	0.037	-0.57
UC (n=25)	18.0	6.7	16.4	7.7	-1.5	-3.3 to 0.3				
Fatigue (0-52)										
HIIT (n=25)	43.6	6.6	46.0	4.3	2.5	0.1 to 4.9	3.2	0.4 to 6.1	0.029	0.48
UC (n=25)	45.3	4.7	44.6	6.0	-0.6	-2.7 to 1.4				
Self-esteem (4-40)										
HIIT (n=25)	34.2	3.4	36.4	3.1	2.2	1.0 to 3.4	3.1	0.9 to 5.3	0.007	0.69
UC (n=25)	33.6	5.3	33.2	5.9	-0.4	-2.2 to 1.4				

A higher value indicates worse psychosocial status for anxiety, depression, and stress and better psychosocial status for fatigue and self-esteem. Anxiety, depression, stress, fatigue, and self-esteem were measured using the State-Trait Anxiety Inventory (STAI), the Center for Epidemiologic Studies-Depression Scale (CES-D), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), the Perceived Stress Scale (PSS), and the Rosenberg Self-Esteem Scale (RSES). Between-group difference at postintervention was analyzed using analysis of covariance adjusting for marital status, employment status, and baseline value of the outcome. SD, standard deviation; CI, confidence interval; HIIT, high-intensity interval training; UC, usual care.

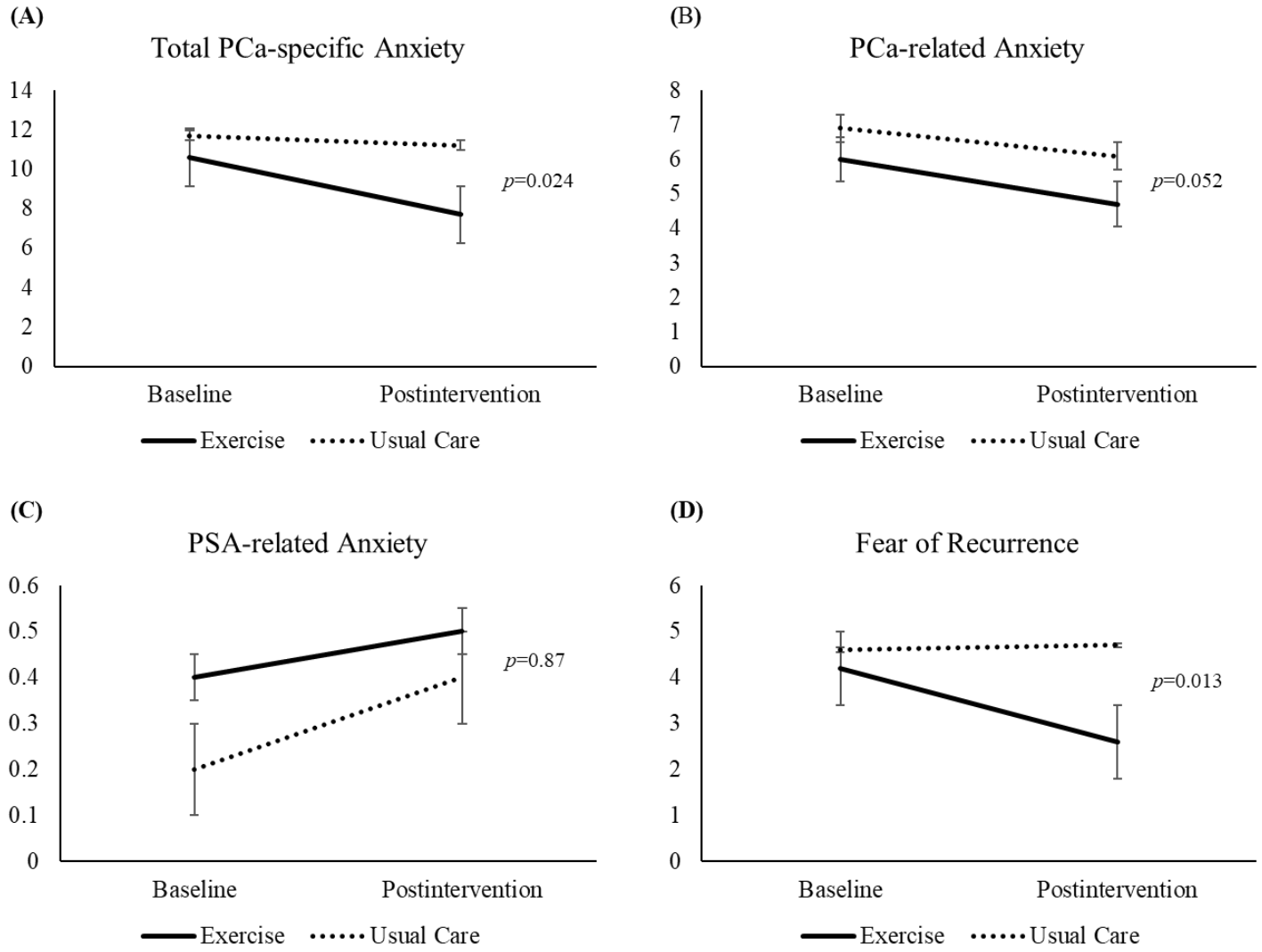


Figure 5-1. Effects of exercise on prostate cancer-specific anxiety in prostate cancer patients on active surveillance in the ERASE trial. *p*-values indicate between-group difference at postintervention using analysis of covariance adjusting for marital status, employment status, and baseline value of the outcome. Error bars indicate standard error. PCa, prostate caner; PSA, prostate-specific antigen.

CHAPTER 6 – DISCUSSION

6.1 Overview

The aim of this dissertation was to investigate the effects of high-intensity interval training (HIIT) on cardiopulmonary and physical fitness, biochemical progress of prostate cancer, cancer-related biomarkers, and patient-reported outcomes in men with prostate cancer (PCa) on active surveillance (AS). To summarize, **Chapter 1** and **Appendix A and B** reviewed current clinical practice in managing low-risk PCa including AS and up-to-date literature on behaviour intervention trials in AS settings. **Chapter 2** and **Appendix E** described the development of the ERASE Trial, including the rationale, design, and detailed study protocol. The primary findings of the ERASE Trials were reported in **Chapter 3** that HIIT exerted significant improvements in cardiopulmonary fitness and biochemical progression on PCa. **Chapter 4** further reported that HIIT reduced several circulating lipid and inflammatory markers, which provides mechanistic evidence that exercise could reduce the risks of cardiovascular disease and PCa progression in PCa patients on AS. Lastly, **Chapter 5** showed that HIIT reduced clinically important psychological outcomes such as PCa-related anxiety and fear of cancer progression as well as improved fatigue, self-esteem, and perceived stress.

As illustrated in **Figure 2-1**, I proposed that physiological conditioning through a 12-week HIIT program, which is an improvement in cardiopulmonary fitness, would yield positive changes in cancer-related biomarkers, patient-reported outcomes, and overall physical and functional fitness. As hypothesized, HIIT yielded an improvement in cardiorespiratory fitness, although the magnitude of the effect did not reach the target effect size (1.6 $ml \cdot kg^{-1} \cdot min^{-1}$ vs. 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$). For the biological pathway, the study found the improvements in biochemical progression of prostate tumour, several inflammatory cytokines, and lipid profiles, while no changes were found in selected metabolic biomarkers. Further assays for other metabolic

outcomes (i.e., insulin, insulin-like growth factor (IGF)-axis, adiponectin, and leptin) and immune markers (i.e., natural killer cell counts and cytotoxic activity), and PCa cell line (i.e., LNCaP) are still in progress and the results will be reported in the future. Also, further statistical analyses will identify whether circulating immune or inflammatory markers were associated with the PCa biochemical and cell line outcomes. For the psychological pathway, HIIT reduced anxiety and fear of cancer progression, which potentially induced a non-significant but meaningful improvement in quality of life. For the functional pathway, HIIT improved a few functional fitness outcomes such as upper body strength and lower body flexibility. Taken together, the ERASE Trial suggests for the first time the potential clinical utility of exercise in addressing disease-related and psychological concerns for PCa patients undergoing AS. Additional results from the ERASE Trial on biomarkers that are currently being analyzed and 1-year follow-up patient-reported and clinical outcomes will further provide important evidence of the effects of HIIT in PCa patients on AS.

6.2 Strengths and Limitations

The strengths and limitations of the ERASE Trial have been discussed in each chapter with regards to the study outcomes of each paper. In this section, I will further expand the key strengths and limitations of the ERASE Trial. The primary strength of the ERASE Trial is its novelty in three aspects: First, it is one of the few randomized controlled trials testing the effects of an isolated exercise intervention in the AS setting. Previous exercise interventions in PCa patient on AS have been part of a multicomponent package which do not allow for the evaluation of the independent effects of exercise. Moreover, most previous trials involving isolated exercise interventions in PCa patients have focused on patients during or after treatments, particularly

androgen deprivation therapy. Findings from patients receiving or recovering from active treatments are unable to answer the unique questions related to AS including disease progression, fear of cancer progression, and preparation for treatments. To date, only one study has tested an exercise intervention in AS patients; however, it focused on the feasibility of exercise during AS and was not able to provide the efficacy of the intervention compared to the control counterpart.

Second, our study is the first clinical trial to examine the effect of exercise on clinical outcomes (i.e., biochemical progression) in relation to existing biological mechanisms. Epidemiological studies have shown a positive association between physical activity and PCa survival. In recent years, pre-clinical studies have suggested a potential impact of exercise on prostate tumour growth and metastasis various biological mechanisms; however, this question has not been studied in a clinical setting. The ERASE Trial measured biochemical progression of disease in addition to metabolic, inflammatory, and immune markers for a comprehensive understanding of the exercise mechanisms of anti-tumour effects. In this dissertation, we have reported the changes of biochemical progression (i.e., PSA and PSA kinetics), sex hormone (i.e., testosterone) and cardiometabolic/inflammatory markers. Other PCa-related biomarkers including PCa cell line (LNCaP), immune activity (i.e., NK cell counts and NK cell cytotoxic activity), and additional metabolic markers (i.e., IGF-axis, adiponectin, and leptin) are currently assayed and analyzed, and the findings will be published in the future. Furthermore, the ERASE Trial includes follow-up up to 1-year after the intervention period for biochemical and biopsy-based PCa progression as well as clinical events, which will provide preliminary evidence of the longer-term effect of HIIT on important clinical outcomes.

Third, ERASE was the first exercise randomized controlled trial that examined fear of cancer progression in AS settings. Fear of cancer progression is emerging as a major unmet

psychosocial need in PCa patients that can undermine quality of life and may even prompt unnecessary medical intervention. As a unique psychological construct, fear of cancer progression is strongly related to overall quality of life and is a major concern during both pre-treatment (i.e., fear of progression) and survivorship (i.e., fear of recurrence). Given the unique AS setting where patients are living with untreated tumours for months to years, it is especially important to alleviate possible fear of PCa progression due to its implication on quality of life and clinical decision. Unfortunately, no intervention during AS has been studied for fear of PCa progression nor implemented in most clinical settings. The ERASE Trial comprehensively examined the effects of exercise on PCa-specific and generic fear of cancer progression in relation to anxiety.

There are other important strengths of the ERASE Trial based on the high-quality study design and implementation: (1) the study design was developed through a comprehensive model as illustrated in **Chapter 2**. I have proposed the multidimensional benefits of exercise in men with PCa on AS in three distinct pathways (i.e., biological, psychological, and functional pathways) that possess clinically-relevant and long-term implications (e.g., time on AS and cost-effectiveness); (2) HIIT, as one type of exercise modality, was selected to maximize the proposed benefits of exercise based on the current evidence as described in **Chapter 2** and supervised HIIT was well-implemented with high adherence (96%) and compliance (100%) to the exercise protocol; (3) the ERASE Trial employed a gold-standard measure for the primary outcome of cardiopulmonary fitness (i.e., VO_{2peak} using a metabolic cart), comprehensive PCa-related biomarkers, and validated patient-reported outcome measures; (4) the ERASE Trial achieved minimal loss of follow-up at post intervention for the primary outcome of VO_{2peak} (88%) and the secondary outcomes of biomarkers, functional fitness, and patient-reported

outcomes (94%); and (5) the ERASE trial incorporated postintervention follow-up period for a year on medical records (e.g., PCa progression and clinical events) and patient-reported outcomes (e.g., fear of cancer progression and exercise behaviour). To date, I have obtained 6-month and 12-month follow-up data from 90% (43/48) and 85% (28/33) of the study participants and the follow-up data collection is expected to be completed by April 2021. Once completed, it would provide important information on whether there are any longer-term effects of HIIT on psychosocial outcomes, exercise behaviours, and PCa progression.

Several important limitations exist in the ERASE Trial, which should be taken into account for the interpretation and application of the findings. First, the ERASE Trial did not reach the targeted sample size of 66 (52/66; 79%) due to slower recruitment. This smaller sample size would still have led to limited power to detect statistically significant differences between groups. Therefore, cautions are needed to interpret the findings in that there is a possibility of chance finding due to between-group imbalances at baseline, outliers, or unknown factors. The ERASE trial had 80% of the target sample size and employed robust statistical methods (i.e., elimination of extreme outliers, and analysis of covariance to adjust identified baseline imbalances), which would have minimized potential chance findings.

Second, potential selection bias in the recruitment of the study participants may exist. In the ERASE trial, eligible PCa patients on AS were provided with the study information in person or via phone call and interested patients participated in the study. Among 176 patients who were eligible and approached by study coordinators, only 30% participated in the trial and about 56% were not interested, including those who expressed no interest (30%) and did not respond to the follow-up phone calls (26%). It means that the majority of our study participants were already

keen on participating in exercise, which may not represent the entire PCa patients on AS and thereby limit the generalizability of the study findings.

Third, postintervention assessments for the health-related fitness and patient-reported outcomes may have influenced by potential bias from the lack of blinding to group assignment for study participants, outcome assessors, and exercise program interventionists. Due to the nature of exercise intervention, it was not possible for study participants to be blinded to group assignment. For example, a systemic review in 12 non-conventional medicine clinical trials reported that non-blinded patients had an exaggeration of the effect size by an average of 0.56 standard deviation in patient-reported outcomes [1]. Also, due to the limited source of staff and logistic issues, we were not able to have separate personnel for outcome assessments and exercise intervention. Group assignment was revealed to participants, outcome assessors, and interventionists at the time of the completion of baseline assessments, and this may have induced potential bias in postintervention assessments. To minimize the potential bias, the outcome assessors in the ERASE trial strictly followed the standardized assessment protocols for the fitness outcomes. Also, study participants, outcome assessors, interventionists were blinded to group assignment for other study outcomes such as biomarkers and medical records.

Lastly, our cross-over design has the potential to contaminate the findings at a 6-month and 12-month follow-up. In the ERASE trial, participants in the UC group were offered a 4-week complimentary HIIT program at our facility and a 12-week community-based exercise program after the 12-week intervention period. This strategy potentially allowed us to maximize recruitment (i.e., ensuring exercise programs regardless of their group assignments) and minimize drop-outs (i.e., exercise programs given after the intervention period). However, more than half (54%) of participants in the UC group were given the 4-week supervised HIIT program,

which may also influence our long-term patient-reported and medical outcomes especially given the potential lingering effects of the 4-week program on their exercise behaviours.

6.3 Future Research Directions

There are several insights that the ERASE Trial can offer for future exercise oncology research in AS settings. The findings from the ERASE Trial inform larger phase trials to confirm the benefits of exercise in men on AS, focusing on long-term oncological outcomes. One of the most important lines of inquiry for patients on AS is how to avoid unnecessary treatments or lengthen the time on AS without compromising survival. Although the survival benefits of AS compared to active treatment has appeared inconsistent across studies [2], the 10-year disease-free survival rate among AS patients is still as high as 95% regardless of treatment strategies [3]. Interestingly, more recent findings from two large randomized controlled trials, the Prostate Testing for Cancer and Treatment (ProtecT) trial [3] and the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) trial [4], agreed that active monitoring showed higher risks of disease progression and metastasis while having low PCa symptoms compared to radical prostatectomy or radiation therapy. Therefore, future exercise oncology trials in AS settings may focus on AS-related clinical concerns such as biochemical or pathological progression of PCa (i.e., PSA, PSA kinetics, and tumour profile), disease reclassification or time to radical treatment, post-treatment side effects (i.e., prehabilitative effect), and early onset of metastasis. For example, Galvao et al. have been conducting a multi-centre randomized controlled trial in AS patients to investigate the effects of a 3-year progressive stepped-down exercise intervention on the time to active treatment [5], which will provide important evidence on clinical outcomes. The ERASE Trial will report 1-year follow-up data on exploratory PCa and clinical outcomes and it

would further bridge the gap between short- and long-term clinical effects of exercise in AS patients.

On a similar note, another aspect to consider is the feasibility of recruitment and intervention delivery with regards to the efficacy-effectiveness spectrum. For example, the design of the ERASE Trial has mixed components to address the efficacy of the intervention (e.g., interested in and medically cleared for high-intensity exercise, living in a specific urban area, individualized HIIT program, supervised setting, and no cost involved for a gym membership or travelling) as well as effectiveness (e.g., relatively radical recruitment criteria such as the inclusion of men with PCa on AS regardless baseline PSA levels or Gleason Score and those who were engaged in moderate-intensity exercise). However, future exercise oncology trials in AS settings that involve long-term clinical outcomes and larger sample sizes should consider various ways of intervention delivery to optimize recruitment. For instance, Parsons et al. conducted the Men's Eating and Living (MEAL) study [6], a phase III randomized controlled trial examining the effects of a behavioural intervention (i.e., vegetable diet) on clinical outcomes in men with PCa on AS. They found no significant reduction in the primary outcome of time to PCa progression at 24-month follow-up in the diet group compared to the control group; however, it was notable that they achieved a high accrual rate (103%; 478/464) over approximately 4 years with minimal dropouts (7%; 35/478). Also, their national-wide telephone-based behavioural change intervention resulted in a substantial increase in vegetable consumption that persisted for two years of the intervention period [7]. This may inform that recruitment of a large sample to detect clinical outcomes would be feasible in AS settings and this was partly possible due to the easy accessibility to the intervention. Therefore, distance-based (e,g., telephone) intervention modality can be considered as a viable option for larger

effectiveness trials such as the Breast cancer Weight Loss (BWEL) study [8] examining the effects of a telephone-based lifestyle intervention (including physical activity) on cancer outcomes in early-stage breast cancer patients.

Another aspect to consider is exercise modality. In the ERASE trial, HIIT intervention was performed only on a treadmill, which was either jogging or fast-paced walking on a higher incline. Notably, 60% of participants had at least one type of joint arthritis or arthralgia at baseline and nearly one-fourth of participants in the HIIT group reported aggravation of their joint issues (e.g., knee or ankle) during the intervention period. Consequently, HIIT on a treadmill might have worsened the previous joint pain, although it is unclear from previous literature likely due to poorly recorded/reported adverse events [9, 10]. In the ERASE Trial, although speed and incline were modified to minimize joint pain without reducing the exercise intensity corresponding to the target VO_{2peak}. Therefore, given that the average age of men diagnosed with low-risk localized PCa is between 60-70 years, other modalities of exercise using a bike, row, or elliptical would be able to address possible joint issues that might have been caused by body weight-based exercise such as jogging or incline walking on a treadmill.

The biological mechanisms that exercise could suppress PCa tumour growth or metastasis are unclear; however, one of the most plausible mechanisms would include increased cancer surveillance. Recent evidence suggests that one key pathway is an enhanced innate immune function based on natural killer (NK) cell activity, accounting for more than 50% of tumour suppression [11]. NK cells, as central components of the first-line innate immunity, play important roles in inhibiting tumour proliferation and promoting apoptosis, and in recent years, therapies aimed at increasing the number and/or function of NK cells have been tested for a role in immune surveillance [12] and immunotherapy [13]. NK cell cytotoxic activity (NKCA) is an

indicator of NK function and poorer NKCA is present in higher stage PCa patients (e.g., approximately 40% and 65% lower in low- and high-grade PCa patients, respectively, compared to healthy counterparts) [14, 15]. A meta-analysis showed that exercise increases NKCA levels up to fourfold compared to resting values, and long-term exercise training also induces elevated basal NKCA levels up to 1.5 fold [16]. Therefore, it is plausible that exercise can induce systemic NKCA numbers and function and inhibit tumour progression in patients with PCa during AS [17]. In the ERASE Trial, further assays in immune profiles including NK cell counts and NKCA are currently in progress and these findings would provide important information on the potential mechanisms between exercise and PCa progression.

Lastly, further research is needed in cancer prehabilitation settings. In recent years, the importance of prehabilitative interventions for cancer patients has been emerging [18]. Potential advantages of cancer prehabilitation include decreased morbidity, improved physical and psychological health, the increased number of available treatment options, decreased hospital stay and readmissions, and reduced direct and indirect cancer-related healthcare costs [19]. Physical exercise can be one of the crucial components in unimodal or multimodal cancer rehabilitation programs [20]; however, as Courneya and Friedenreich noted in their article describing the Physical Exercise Across the Cancer Experience Framework [21], only minimal attention has been paid to exercise during the pre-treatment period for cancer control outcomes [18]. To date, several studies have investigated the effects of “prehabilitation” exercise interventions [22] including exercise trials in lung cancer [23-28], colorectal cancer [29-32], PCa [33, 34], and breast cancer patients [35]. Most of these studies, however, are conducted presurgical or preoperative settings where only a limited period between a cancer diagnosis and curative treatments from several days to several weeks. Low-risk cancer patient groups with an

extended “prehabilitation” period, such as PCa patients on AS, present unique unmet clinical needs as described in **Chapter 1 and 2**. AS practice has been introduced to other cancer types other than PCa such as early-stage breast cancer or ductal carcinoma in situ (DCIS) and thyroid cancer, and the number of cancer patients who choose AS is increasing [36]. Exercise interventions in these unique cancer groups on AS may provide not only evidence on potential clinical and phycological benefits of exercise but also opportunities for exercise oncologists to further identify the impacts of exercise on existing tumours in clinical settings.

6.4 Practical Implications

In most of the current AS practices, patients are not offered any guidance that may potentially reduce the risk of PCa progression or psychological distress such as fear of cancer progression. It is reported that there is a lack of reliable PCa resources and many men on AS and care providers seek information or guidance such as lifestyle modifications [37, 38]. Although the clinical benefits of exercise in AS settings are needed to be confirmed from larger trials, the findings from the ERASE Trial suggest that high-intensity aerobic exercise can be a cost-effective intervention to improve physical fitness and psychological distress during AS. If exercise were further shown to suppress PCa progression, reduce the risk of metastasis, and ultimately improve long-term survival, it would represent a critical advance in the supportive care of PCa patients receiving AS. Therefore, men with PCa undergoing AS would be benefited from HIIT by improving physical fitness and psychological distress, and further research still is warranted to determine whether exercise could benefit long-term oncologic prognosis.

6.5 Conclusion

This dissertation aimed to provide scientific evidence on the effects of exercise on fitness, biological, and psychological outcomes in men with PCa on AS. The findings of the ERASE Trial demonstrated that HIIT improved cardiopulmonary fitness, biochemical progression of PCa, systemic lipid and inflammatory markers, and psychological outcomes compared to UC. Larger phase II/III trials are required to confirm our findings and further investigate the long-term clinical outcomes. Lastly, the strengths and limitations of the ERASE Trial should be taken into account in the interpretation and application of the study findings as well as would provide guidance to future exercise oncology research in AS settings.

6.6 References

1. Hróbjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, and Brorson S, Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. *International journal of epidemiology*, 2014. **43**(4): p. 1272-83.
2. Vernooij RWM, Lancee M, Cleves A, Dahm P, Bangma CH, and Aben KKH, Radical prostatectomy versus deferred treatment for localised prostate cancer. *Cochrane Database of Systematic Reviews*, 2020(6).
3. Neal DE, Metcalfe C, Donovan JL, Lane JA, Davis M, Young GJ, et al., Ten-year Mortality, Disease Progression, and Treatment-related Side Effects in Men with Localised Prostate Cancer from the ProtecT Randomised Controlled Trial According to Treatment Received. *European Urology*, 2020. **77**(3): p. 320-30.
4. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, et al., Radical Prostatectomy or Watchful Waiting in Prostate Cancer — 29-Year Follow-up. *New England Journal of Medicine*, 2018. **379**(24): p. 2319-29.
5. Galvao DA, Hayne D, Frydenberg M, Chambers SK, Taaffe DR, Spry N, et al., Can exercise delay transition to active therapy in men with low-grade prostate cancer? A multicentre randomised controlled trial. *BMJ Open*, 2018. **8**(4): p. e022331.
6. Parsons JK, Pierce JP, Mohler J, Paskett E, Jung S-H, Humphrey P, et al., A randomized trial of diet in men with early stage prostate cancer on active surveillance: rationale and design of the Men's Eating and Living (MEAL) Study (CALGB 70807 [Alliance]). *Contemporary clinical trials*, 2014. **38**(2): p. 198-203.

7. Parsons JK, Zahrieh D, Mohler JL, Paskett E, Hansel DE, Kibel AS, et al., Effect of a Behavioral Intervention to Increase Vegetable Consumption on Cancer Progression Among Men With Early-Stage Prostate Cancer: The MEAL Randomized Clinical Trial. *JAMA*, 2020. **323**(2): p. 140-8.

8. Ligibel JA, Barry WT, Alfano C, Hershman DL, Irwin M, Neuhouser M, et al., Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early breast cancer (Alliance A011401): study design. *NPJ Breast Cancer*, 2017. **3**: p. 37.

9. Regnaux JP, Lefevre-Colau MM, Trinquart L, Nguyen C, Boutron I, Brosseau L, et al., High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. *Cochrane Database of Systematic Reviews*, 2015(10).

10. Mugele H, Freitag N, Wilhelmi J, Yang Y, Cheng S, Bloch W, et al., High-intensity interval training in the therapy and aftercare of cancer patients: a systematic review with meta-analysis. *Journal of Cancer Survivorship*, 2019. **13**(2): p. 205-23.

11. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al., Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. *Cell Metab*, 2016. **23**(3): p. 554-62.

12. Waldhauer I and Steinle A, NK cells and cancer immunosurveillance. *Oncogene*, 2008. **27**(45): p. 5932-43.

13. Guillerey C, Huntington ND, and Smyth MJ, Targeting natural killer cells in cancer immunotherapy. *Nat Immunol*, 2016. **17**(9): p. 1025-36.

14. Tarle M, Kraljic I, and Kastelan M, Comparison between Nk Cell-Activity and Prostate-Cancer Stage and Grade in Untreated Patients - Correlation with Tumor-Markers and Hormonal Serotest Data. *Urological Research*, 1993. **21**(1): p. 17-21.

15. Choe BK, Frost P, Morrison MK, and Rose NR, Natural killer cell activity of prostatic cancer patients. *Cancer Invest*, 1987. **5**(4): p. 285-91.

16. Shephard RJ and Shek PN, Effects of exercise and training on natural killer cell counts and cytolytic activity: a meta-analysis. *Sports Med*, 1999. **28**(3): p. 177-95.

17. Idorn M and Thor Straten P, Exercise and cancer: from "healthy" to "therapeutic"? *Cancer Immunol Immunother*, 2017. **66**(5): p. 667-71.

18. Silver JK and Baima J, Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *American Journal of Physical Medicine & Rehabilitation*, 2013. **92**(8): p. 715-27.

19. Silver JK. *Cancer prehabilitation and its role in improving health outcomes and reducing health care costs*. in *Seminars in oncology nursing*. 2015. Elsevier.

20. Loughney L and Grocott MP, Exercise and Nutrition Prehabilitation for the Evaluation of Risk and Therapeutic Potential in Cancer Patients: A Review. *Int Anesthesiol Clin*, 2016. **54**(4): p. e47-61.

21. Courneya KS and Friedenreich CM, Framework PEACE: an organizational model for examining physical exercise across the cancer experience. *Ann Behav Med*, 2001. **23**(4): p. 263-72.

22. Faithfull S, Turner L, Poole K, Joy M, Manders R, Weprin J, et al., Prehabilitation for adults diagnosed with cancer: A systematic review of long-term physical function,

nutrition and patient-reported outcomes. *European Journal of Cancer Care*, 2019. **28**(4): p. e13023.

23. Brunelli A, Pompili C, Berardi R, Mazzanti P, Onofri A, Salati M, et al., Performance at preoperative stair-climbing test is associated with prognosis after pulmonary resection in stage I non-small cell lung cancer. *Ann Thorac Surg*, 2012. **93**(6): p. 1796-800.

24. Pehlivan E, Turna A, Gurses A, and Gurses HN, The effects of preoperative short-term intense physical therapy in lung cancer patients: a randomized controlled trial. *Ann Thorac Cardiovasc Surg*, 2011. **17**(5): p. 461-8.

25. Bobbio A, Chetta A, Ampollini L, Primomo GL, Internullo E, Carbognani P, et al., Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. *Eur J Cardiothorac Surg*, 2008. **33**(1): p. 95-8.

26. Cesario A, Ferri L, Galetta D, Cardaci V, Biscione G, Pasqua F, et al., Pre-operative pulmonary rehabilitation and surgery for lung cancer. *Lung Cancer*, 2007. **57**(1): p. 118-9.

27. Sekine Y, Chiyo M, Iwata T, Yasufuku K, Furukawa S, Amada Y, et al., Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. *Jpn J Thorac Cardiovasc Surg*, 2005. **53**(5): p. 237-43.

28. Nagarajan K, Bennett A, Agostini P, and Naidu B, Is preoperative physiotherapy/pulmonary rehabilitation beneficial in lung resection patients? *Interactive cardiovascular and thoracic surgery*, 2011. **13**(3): p. 300-2.

29. Boereboom CL, Williams JP, Leighton P, Lund JN, and Exercise Prehabilitation in Colorectal Cancer Delphi Study G, Forming a consensus opinion on exercise

prehabilitation in elderly colorectal cancer patients: a Delphi study. *Tech Coloproctol*, 2015. **19**(6): p. 347-54.

30. Chen BP, Awasthi R, Sweet SN, Minnella EM, Bergdahl A, Santa Mina D, et al., Four-week prehabilitation program is sufficient to modify exercise behaviors and improve preoperative functional walking capacity in patients with colorectal cancer. *Support Care Cancer*, 2017. **25**(1): p. 33-40.
31. Singh F, Newton RU, Baker MK, Spry NA, Taaffe DR, and Galvao DA, Feasibility and Efficacy of Presurgical Exercise in Survivors of Rectal Cancer Scheduled to Receive Curative Resection. *Clin Colorectal Cancer*, 2017. **16**(4): p. 358-65.
32. Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P, et al., Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery. *Surgery*, 2011. **150**(3): p. 505-14.
33. Santa Mina D, Matthew AG, Hilton WJ, Au D, Awasthi R, Alibhai SM, et al., Prehabilitation for men undergoing radical prostatectomy: a multi-centre, pilot randomized controlled trial. *BMC Surg*, 2014. **14**(1): p. 89.
34. Singh F, Newton RU, Baker MK, Spry NA, Taaffe DR, Thavaseelan J, et al., Feasibility of Presurgical Exercise in Men With Prostate Cancer Undergoing Prostatectomy. *Integr Cancer Ther*, 2017. **16**(3): p. 290-9.
35. Ligibel JA, Dillon D, Giobbie-Hurder A, McTiernan A, Frank E, Cornwell M, et al., Impact of a Pre-Operative Exercise Intervention on Breast Cancer Proliferation and Gene Expression: Results from the Pre-Operative Health and Body (PreHAB) Study. *Clin Cancer Res*, 2019. **25**(17): p. 5398-406.

36. Haymart MR, Miller DC, and Hawley ST, Active Surveillance for Low-Risk Cancers - A Viable Solution to Overtreatment? *The New England journal of medicine*, 2017. **377**(3): p. 203-6.

37. Loeb S, Curnyn C, Fagerlin A, Braithwaite RS, Schwartz MD, Lepor H, et al., Informational needs during active surveillance for prostate cancer: A qualitative study. *Patient Educ Couns*, 2018. **101**(2): p. 241-7.

38. Fitch M, Pang K, Ouellet V, Loiselle C, Alibhai S, Chevalier S, et al., Canadian Men's perspectives about active surveillance in prostate cancer: need for guidance and resources. *BMC Urol*, 2017. **17**(1): p. 98.

BIBLIOGRAPHY

1. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al., The European-Organization-for-Research-and-Treatment-of-Cancer Qlq-C30 - a Quality-of-Life Instrument for Use in International Clinical-Trials in Oncology. *Journal of the National Cancer Institute*, 1993. **85**(5): p. 365-76.
2. Adams SC, DeLorey DS, Davenport MH, Fairey AS, North S, and Courneya KS, Effects of high-intensity interval training on fatigue and quality of life in testicular cancer survivors. *Br J Cancer*, 2018. **118**(10): p. 1313-21.
3. Adams SC, DeLorey DS, Davenport MH, Stickland MK, Fairey AS, North S, et al., Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: A phase 2 randomized controlled trial. *Cancer*, 2017. **123**(20): p. 4057-65.
4. Ajzen I, The theory of planned behavior. *Organizational behavior and human decision processes*, 1991. **50**(2): p. 179-211.
5. *Alberta Cancer Exercise (ACE) Program*. Available from: https://www.albertacancerexercise.com/.
6. American College of Sports Medicine, *ACSM's guidelines for exercise testing and prescription*. 2013: Lippincott Williams & Wilkins.
7. Arlen PM, Bianco F, Dahut WL, D'Amico A, Figg WD, Freedland SJ, et al., Prostate Specific Antigen Working Group Guidelines on Prostate Specific Antigen Doubling Time. *Journal of Urology*, 2008. **179**(6): p. 2181-6.
8. Ashcraft KA, Peace RM, Betof AS, Dewhirst MW, and Jones LW, Efficacy and Mechanisms of Aerobic Exercise on Cancer Initiation, Progression, and Metastasis: A

Critical Systematic Review of In Vivo Preclinical Data. *Cancer Res*, 2016. **76**(14): p. 4032-50.

9. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, and Alfano CM, Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *Journal of the National Cancer Institute*, 2012. **104**(11): p. 815-40.
10. Banerjee S, Manley K, Shaw B, Lewis L, Cucato G, Mills R, et al., Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a feasibility randomised controlled trial. *Support Care Cancer*, 2018. **26**(5): p. 1515-23.
11. Barocas DA, Alvarez J, Resnick MJ, Koyama T, Hoffman KE, Tyson MD, et al., Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. *JAMA*, 2017. **317**(11): p. 1126-40.
12. Beltz NM, Gibson AL, Janot JM, Kravitz L, Mermier CM, and Dalleck LC, Graded Exercise Testing Protocols for the Determination of VO2max: Historical Perspectives, Progress, and Future Considerations. *J Sports Med (Hindawi Publ Corp)*, 2016. **2016**: p. 3968393.
13. Bent R, Moll L, Grabbe S, and Bros M, Interleukin-1 beta—a friend or foe in malignancies? *International journal of molecular sciences*, 2018. **19**(8): p. 2155.
14. Bigaran A, Zopf E, Gardner J, La Gerche A, Murphy DG, Howden EJ, et al., The effect of exercise training on cardiometabolic health in men with prostate cancer receiving androgen deprivation therapy: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*, 2020.
15. Bigley AB and Simpson RJ, NK cells and exercise: implications for cancer immunotherapy and survivorship. *Discov Med*, 2015. **19**(107): p. 433-45.

16. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, et al., Radical Prostatectomy or Watchful Waiting in Prostate Cancer — 29-Year Follow-up. *New England Journal of Medicine*, 2018. **379**(24): p. 2319-29.

17. Biro PA, Thomas F, Ujvari B, and Beckmann C, Can Energetic Capacity Help Explain Why Physical Activity Reduces Cancer Risk? *Trends in cancer*, 2020.

18. Bobbio A, Chetta A, Ampollini L, Primomo GL, Internullo E, Carbognani P, et al., Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. *Eur J Cardiothorac Surg*, 2008. **33**(1): p. 95-8.

19. Boereboom CL, Williams JP, Leighton P, Lund JN, and Exercise Prehabilitation in Colorectal Cancer Delphi Study G, Forming a consensus opinion on exercise prehabilitation in elderly colorectal cancer patients: a Delphi study. *Tech Coloproctol*, 2015. **19**(6): p. 347-54.

20. Bonn SE, Sjolander A, Lagerros YT, Wiklund F, Stattin P, Holmberg E, et al., Physical activity and survival among men diagnosed with prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 2015. **24**(1): p. 57-64.

21. Borm GF, Fransen J, and Lemmens WA, A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol*, 2007. **60**(12): p. 1234-8.

22. Bourke L, Smith D, Steed L, Hooper R, Carter A, Catto J, et al., Exercise for Men with Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol*, 2016. **69**(4): p. 693-703.

23. Bourke L, Smith D, Steed L, Hooper R, Carter A, Catto J, et al., Exercise for men with prostate cancer: a systematic review and meta-analysis. *European urology*, 2016. **69**(4): p. 693-703.

24. Bourke L, Stevenson R, Turner R, Hooper R, Sasieni P, Greasley R, et al., Exercise training as a novel primary treatment for localised prostate cancer: a multi-site randomised controlled phase II study. *Sci Rep*, 2018. **8**(1): p. 8374.

25. Brunelli A, Pompili C, Berardi R, Mazzanti P, Onofri A, Salati M, et al., Performance at preoperative stair-climbing test is associated with prognosis after pulmonary resection in stage I non-small cell lung cancer. *Ann Thorac Surg*, 2012. **93**(6): p. 1796-800.

26. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al., Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. *Cancer Treat Rev*, 2017. **52**: p. 91-104.

27. Bul M, Zhu X, Rannikko A, Staerman F, Valdagni R, Pickles T, et al., Radical prostatectomy for low-risk prostate cancer following initial active surveillance: results from a prospective observational study. *Eur Urol*, 2012. **62**(2): p. 195-200.

28. Burdon JG, Juniper EF, Killian KJ, Hargreave FE, and Campbell EJ, The perception of breathlessness in asthma. *Am Rev Respir Dis*, 1982. **126**(5): p. 825-8.

29. Burton AJ, Martin RM, Donovan JL, Lane JA, Davis M, Hamdy FC, et al., Associations of lifestyle factors and anthropometric measures with repeat PSA levels during active surveillance/monitoring. *Cancer Epidemiol Biomarkers Prev*, 2012. **21**(10): p. 1877-85.

30. Cadmus LA, Salovey P, Yu H, Chung G, Kasl S, and Irwin ML, Exercise and quality of life during and after treatment for breast cancer: results of two randomized controlled trials. *Psychooncology*, 2009. **18**(4): p. 343-52.

31. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al., Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc*, 2019. **51**(11): p. 2375-90.

32. Campo RA, Agarwal N, LaStayo PC, O'Connor K, Pappas L, Boucher KM, et al., Levels of fatigue and distress in senior prostate cancer survivors enrolled in a 12-week randomized controlled trial of Qigong. *Journal of Cancer Survivorship*, 2014. **8**(1): p. 60-9.

33. Canadian Cancer Society, *Canadian Cancer Statistics 2019*. 2019.

34. Cardozo GG, Oliveira RB, and Farinatti PT, Effects of high intensity interval versus moderate continuous training on markers of ventilatory and cardiac efficiency in coronary heart disease patients. *ScientificWorldJournal*, 2015. **2015**: p. 192479.

35. Carter HB, Ferrucci L, Kettermann A, Landis P, Wright EJ, Epstein JI, et al., Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst*, 2006. **98**(21): p. 1521-7.

36. Cella D, Eton DT, Lai JS, Peterman AH, and Merkel DE, Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage*, 2002. **24**(6): p. 547-61.

37. Cesario A, Ferri L, Galetta D, Cardaci V, Biscione G, Pasqua F, et al., Pre-operative pulmonary rehabilitation and surgery for lung cancer. *Lung Cancer*, 2007. **57**(1): p. 118-9.

38. Chen BP, Awasthi R, Sweet SN, Minnella EM, Bergdahl A, Santa Mina D, et al., Four-week prehabilitation program is sufficient to modify exercise behaviors and improve

preoperative functional walking capacity in patients with colorectal cancer. *Support Care Cancer*, 2017. **25**(1): p. 33-40.

39. Chen RC, Basak R, Meyer A, and et al., Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. *JAMA*, 2017. **317**(11): p. 1141-50.

40. Chen RC, Basak R, Meyer AM, Kuo TM, Carpenter WR, Agans RP, et al., Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. *JAMA*, 2017. **317**(11): p. 1141-50.

41. Choe BK, Frost P, Morrison MK, and Rose NR, Natural killer cell activity of prostatic cancer patients. *Cancer Invest*, 1987. **5**(4): p. 285-91.

42. Cocks K, King MT, Velikova G, Fayers PM, and Brown JM, Quality, interpretation and presentation of European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 data in randomised controlled trials. *Eur J Cancer*, 2008. **44**(13): p. 1793-8.

43. Cohen S, Kamarck T, and Mermelstein R, A global measure of perceived stress. *J Health Soc Behav*, 1983. **24**(4): p. 385-96.

44. Cohen S, Kamarck T, and Mermelstein R, Perceived stress scale. *Measuring stress: A guide for health and social scientists*, 1994.

45. Cooperberg MR and Carroll PR, Trends in Management for Patients With Localized Prostate Cancer, 1990-2013. *JAMA*, 2015. **314**(1): p. 80-2.

46. Cooperberg MR, Carroll PR, and Klotz L, Active surveillance for prostate cancer: progress and promise. *J Clin Oncol*, 2011. **29**(27): p. 3669-76.

47. Cormie P, Galvão DA, Spry N, Joseph D, Chee R, Taaffe DR, et al., Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU international*, 2015. **115**(2): p. 256-66.

48. Cormie P, Galvão DA, Spry N, Joseph D, Chee R, Taaffe DR, et al., Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU International*, 2015. **115**(2): p. 256-66.

49. Cormie P, Newton RU, Spry N, Joseph D, Taaffe DR, and Galvao DA, Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. *Prostate Cancer Prostatic Dis*, 2013. **16**(4): p. 328-35.

50. Courneya KS and Friedenreich CM, Framework PEACE: an organizational model for examining physical exercise across the cancer experience. *Ann Behav Med*, 2001. **23**(4): p. 263-72.

51. Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, and Fairey AS, Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *J Clin Oncol*, 2003. **21**(9): p. 1660-8.

52. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al., Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol*, 2007. **25**(28): p. 4396-404.

53. Courneya KS, Sellar CM, Stevinson C, McNeely ML, Peddle CJ, Friedenreich CM, et al., Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J Clin Oncol*, 2009. **27**(27): p. 4605-12.

54. Culos-Reed SN, Robinson JW, Lau H, Stephenson L, Keats M, Norris S, et al., Physical activity for men receiving androgen deprivation therapy for prostate cancer: benefits from a 16-week intervention. *Supportive Care in Cancer*, 2010. **18**(5): p. 591-9.

55. Custers JA, van den Berg SW, van Laarhoven HW, Bleiker EM, Gielissen MF, and Prins JB, The Cancer Worry Scale: detecting fear of recurrence in breast cancer survivors. *Cancer Nurs*, 2014. **37**(1): p. E44-50.

56. Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR, et al., Active surveillance for prostate cancer: a systematic review of the literature. *Eur Urol*, 2012. **62**(6): p. 976-83.

57. Dall'Era MA, Konety BR, Cowan JE, Shinohara K, Stauf F, Cooperberg MR, et al., Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer*, 2008. **112**(12): p. 2664-70.

58. Dall'Era MA, The economics of active surveillance for prostate cancer. *Curr Opin Urol*, 2013. **23**(3): p. 278-82.

59. Daubenmier JJ, Weidner G, Marlin R, Crutchfield L, Dunn-Emke S, Chi C, et al., Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance. *Urology*, 2006. **67**(1): p. 125-30.

60. Demark-Wahnefried W, Nix JW, Hunter GR, Rais-Bahrami S, Desmond RA, Chacko B, et al., Feasibility outcomes of a presurgical randomized controlled trial exploring the impact of caloric restriction and increased physical activity versus a wait-list control on

tumor characteristics and circulating biomarkers in men electing prostatectomy for prostate cancer. *BMC Cancer*, 2016. **16**(1): p. 61.

61. Demark-Wahnefried W, Rais-Bahrami S, Desmond RA, Gordetsky JB, Hunter GR, Yang ES, et al., Presurgical weight loss affects tumour traits and circulating biomarkers in men with prostate cancer. *Br J Cancer*, 2017. **117**(9): p. 1303-13.

62. Devin JL, Sax AT, Hughes GI, Jenkins DG, Aitken JF, Chambers SK, et al., The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: a randomised controlled trial. *J Cancer Surviv*, 2016. **10**(3): p. 467-79.

63. Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, et al., Lipid-related markers and cardiovascular disease prediction. *Jama*, 2012. **307**(23): p. 2499-506.

64. Dinkel A and Herschbach P, *Fear of progression in cancer patients and survivors*, in *Psycho-Oncology*. 2018, Springer. p. 13-33.

65. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al., Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1425-37.

66. Dragomir A, Cury FL, and Aprikian AG, Active surveillance for low-risk prostate cancer compared with immediate treatment: a Canadian cost comparison. *CMAJ Open*, 2014. **2**(2): p. E60-8.

67. Eriksen AK, Hansen RD, Borre M, Larsen RG, Jensen JM, Overgaard K, et al., A lifestyle intervention among elderly men on active surveillance for non-aggressive prostate cancer: a randomised feasibility study with whole-grain rye and exercise. *Trials*, 2017. **18**(1): p. 20.

68. Faithfull S, Turner L, Poole K, Joy M, Manders R, Weprin J, et al., Prehabilitation for adults diagnosed with cancer: A systematic review of long-term physical function, nutrition and patient-reported outcomes. *European Journal of Cancer Care*, 2019. **28**(4): p. e13023.

69. Farris MS, Kopciuk KA, Courneya KS, McGregor SE, Wang Q, and Friedenreich CM, Identification and prediction of health-related quality of life trajectories after a prostate cancer diagnosis. *Int J Cancer*, 2017. **140**(7): p. 1517-27.

70. Fitch M, Pang K, Ouellet V, Loiselle C, Alibhai S, Chevalier S, et al., Canadian Men's perspectives about active surveillance in prostate cancer: need for guidance and resources. *BMC Urol*, 2017. **17**(1): p. 98.

71. Frattaroli J, Weidner G, Dnistrian AM, Kemp C, Daubenmier JJ, Marlin RO, et al., Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology*, 2008. **72**(6): p. 1319-23.

72. Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, and Elliott FG, Case-control study of lifetime total physical activity and prostate cancer risk. *Am J Epidemiol*, 2004. **159**(8): p. 740-9.

73. Friedenreich CM, Wang Q, Neilson HK, Kopciuk KA, McGregor SE, and Courneya KS, Physical Activity and Survival After Prostate Cancer. *Eur Urol*, 2016. **70**(4): p. 576-85.

74. Galvao DA, Hayne D, Frydenberg M, Chambers SK, Taaffe DR, Spry N, et al., Can exercise delay transition to active therapy in men with low-grade prostate cancer? A multicentre randomised controlled trial. *BMJ Open*, 2018. **8**(4): p. e022331.

75. Galvao DA, Spry N, Denham J, Taaffe DR, Cormie P, Joseph D, et al., A multicentre year-long randomised controlled trial of exercise training targeting physical functioning

in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. *Eur Urol*, 2014. **65**(5): p. 856-64.

76. Galvao DA, Taaffe DR, Spry N, Joseph D, and Newton RU, Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*, 2010. **28**(2): p. 340-7.

77. George DJ, Halabi S, Shepard TF, Sanford B, Vogelzang NJ, Small EJ, et al., The prognostic significance of plasma interleukin-6 levels in patients with metastatic hormone-refractory prostate cancer: results from cancer and leukemia group B 9480. *Clinical Cancer Research*, 2005. **11**(5): p. 1815-20.

78. Ghasemi A and Zahediasl S, Normality tests for statistical analysis: a guide for non-statisticians. *International journal of endocrinology and metabolism*, 2012. **10**(2): p. 486.

79. Gibala MJ, Little JP, Macdonald MJ, and Hawley JA, Physiological adaptations to low-volume, high-intensity interval training in health and disease. *J Physiol*, 2012. **590**(5): p. 1077-84.

80. Giovannucci EL, Liu Y, Leitzmann MF, Stampfer MJ, and Willett WC, A prospective study of physical activity and incident and fatal prostate cancer. *Arch Intern Med*, 2005. **165**(9): p. 1005-10.

81. Giovannucci EL, Liu Y, Leitzmann MF, Stampfer MJ, and Willett WC, A prospective study of physical activity and incident and fatal prostate cancer. *Archives of internal medicine*, 2005. **165**(9): p. 1005-10.

82. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, and Nimmo MA, The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*, 2011. **11**(9): p. 607-15.

83. Godin G and Shephard R, Godin leisure-time exercise questionnaire. *Med Sci Sports Exerc*, 1997. **29**(6): p. 36-8.

84. Goh AC, Kowalkowski MA, Bailey DE, Jr., Kazer MW, Knight SJ, and Latini DM, Perception of cancer and inconsistency in medical information are associated with decisional conflict: a pilot study of men with prostate cancer who undergo active surveillance. *BJU Int*, 2012. **110**(2 Pt 2): p. E50-6.

85. Guéritat J, Lefeuvre-Orfila L, Vincent S, Crétual A, Ravanat J-L, Gratas-Delamarche A, et al., Exercise training combined with antioxidant supplementation prevents the antiproliferative activity of their single treatment in prostate cancer through inhibition of redox adaptation. *Free Radical Biology and Medicine*, 2014. **77**: p. 95-105.

86. Guillerey C, Huntington ND, and Smyth MJ, Targeting natural killer cells in cancer immunotherapy. *Nat Immunol*, 2016. **17**(9): p. 1025-36.

87. Gupta D, Lee Chuy K, Yang JC, Bates M, Lombardo M, and Steingart RM, Cardiovascular and Metabolic Effects of Androgen-Deprivation Therapy for Prostate Cancer. *J Oncol Pract*, 2018. **14**(10): p. 580-7.

88. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al., 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1415-24.

89. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, and Conde JGJJobi, Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. 2009. **42**(2): p. 377-81.

90. Hayashi T, Fujita K, Matsushita M, and Nonomura N, Main Inflammatory Cells and Potentials of Anti-Inflammatory Agents in Prostate Cancer. *Cancers (Basel)*, 2019. **11**(8).

91. Hayes BD, Brady L, Pollak M, and Finn SP, Exercise and Prostate Cancer: Evidence and Proposed Mechanisms for Disease Modification. *Cancer Epidemiol Biomarkers Prev*, 2016. **25**(9): p. 1281-8.

92. Haymart MR, Miller DC, and Hawley ST, Active Surveillance for Low-Risk Cancers - A Viable Solution to Overtreatment? *The New England journal of medicine*, 2017. **377**(3): p. 203-6.

93. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al., EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol*, 2011. **59**(1): p. 61-71.

94. Helgerud J, Hoydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, et al., Aerobic high-intensity intervals improve VO2max more than moderate training. *Medicine and Science in Sports and Exercise*, 2007. **39**(4): p. 665-71.

95. Hofmann P, Cancer and Exercise: Warburg Hypothesis, Tumour Metabolism and High-Intensity Anaerobic Exercise. *Sports (Basel)*, 2018. **6**(1).

96. Hojman P, Gehl J, Christensen JF, and Pedersen BK, Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. *Cell Metab*, 2018. **27**(1): p. 10-21.

97. Hróbjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, and Brorson S, Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing

patients to blind and nonblind sub-studies. *International journal of epidemiology*, 2014. **43**(4): p. 1272-83.

98. Hvid T, Lindegaard B, Winding K, Iversen P, Brasso K, Solomon TP, et al., Effect of a 2-year home-based endurance training intervention on physiological function and PSA doubling time in prostate cancer patients. *Cancer Causes Control*, 2016. **27**(2): p. 165-74.

99. Idorn M and Hojman P, Exercise-Dependent Regulation of NK Cells in Cancer Protection. *Trends Mol Med*, 2016. **22**(7): p. 565-77.

100. Idorn M and Thor Straten P, Exercise and cancer: from "healthy" to "therapeutic"? *Cancer Immunol Immunother*, 2017. **66**(5): p. 667-71.

101. Idorn M and Thor Straten P, Exercise: A new role for an old tool. *Mol Cell Oncol*, 2016. **3**(4): p. e1163005.

102. Johnsen NF, Tjonneland A, Thomsen BL, Christensen J, Loft S, Friedenreich C, et al., Physical activity and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Int J Cancer*, 2009. **125**(4): p. 902-8.

103. Jones LW, Antonelli J, Masko EM, Broadwater G, Lascola CD, Fels D, et al., Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. *J Appl Physiol (1985)*, 2012. **113**(2): p. 263-72.

104. Jones LW, Hornsby WE, Freedland SJ, Lane A, West MJ, Moul JW, et al., Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized prostate cancer. *Eur Urol*, 2014. **65**(5): p. 852-5.

105. Kampshoff CS, van Dongen JM, van Mechelen W, Schep G, Vreugdenhil A, Twisk JWR, et al., Long-term effectiveness and cost-effectiveness of high versus low-to-

moderate intensity resistance and endurance exercise interventions among cancer survivors. *J Cancer Surviv*, 2018. **12**(3): p. 417-29.

106. Kang DW, Fairey AS, Boulé NG, Field CJ, and Courneya KS, Exercise duRing Active Surveillance for prostatE cancer-the ERASE trial: a study protocol of a phase II randomised controlled trial. *BMJ Open*, 2019. **9**(7): p. e026438.

107. Kang DW, Lee J, Suh SH, Ligibel J, Courneya KS, and Jeon JY, Effects of Exercise on Insulin, IGF Axis, Adipocytokines, and Inflammatory Markers in Breast Cancer Survivors: A Systematic Review and Meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 2017. **26**(3): p. 355-65.

108. Kazzazi A, Momtahen S, Bruhn A, Hemani M, Ramaswamy K, and Djavan B, New findings in localized and advanced prostate cancer: AUA 2011 review. *Can J Urol*, 2011. **18**(3): p. 568398.

109. Keegan KA, Dall'Era MA, Durbin-Johnson B, and Evans CP, Active surveillance for prostate cancer compared with immediate treatment: an economic analysis. *Cancer*, 2012. **118**(14): p. 3512-8.

110. Keilani M, Hasenoehrl T, Baumann L, Ristl R, Schwarz M, Marhold M, et al., Effects of resistance exercise in prostate cancer patients: a meta-analysis. *Support Care Cancer*, 2017. **25**(9): p. 2953-68.

111. Kenfield SA, Chang ST, and Chan JM, Diet and lifestyle interventions in active surveillance patients with favorable-risk prostate cancer. *Curr Treat Options Oncol*, 2007. **8**(3): p. 173-96.

112. Kenfield SA, Stampfer MJ, Giovannucci E, and Chan JM, Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol*, 2011. **29**(6): p. 726-32.

113. Khosravi N, Stoner L, Farajivafa V, and Hanson ED, Exercise training, circulating cytokine levels and immune function in cancer survivors: A meta-analysis. *Brain, Behavior, and Immunity*, 2019. **81**: p. 92-104.

114. Kinsella N, Stattin P, Cahill D, Brown C, Bill-Axelson A, Bratt O, et al., Factors Influencing Men's Choice of and Adherence to Active Surveillance for Low-risk Prostate Cancer: A Mixed-method Systematic Review. *Eur Urol*, 2018. **74**(3): p. 261-80.

115. Klotz L, Active surveillance, quality of life, and cancer-related anxiety. *Eur Urol*, 2013. **64**(1): p. 37-9.

116. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al., Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*, 2009. **301**(19): p. 2024-35.

117. Koelwyn GJ, Wennerberg E, Demaria S, and Jones LW, Exercise in Regulation of Inflammation-Immune Axis Function in Cancer Initiation and Progression. *Oncology (Williston Park)*, 2015. **29**(12): p. 908-20, 22.

118. Lakoski SG, Willis BL, Barlow CE, Leonard D, Gao A, Radford NB, et al., Midlife Cardiorespiratory Fitness, Incident Cancer, and Survival After Cancer in Men: The Cooper Center Longitudinal Study. *JAMA Oncol*, 2015. **1**(2): p. 231-7.

119. Lao C, Edlin R, Rouse P, Brown C, Holmes M, Gilling P, et al., The cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for low risk localised prostate cancer. *BMC Cancer*, 2017. **17**(1): p. 529.

120. Latini DM, Hart SL, Knight SJ, Cowan JE, Ross PL, Duchane J, et al., The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. *J Urol*, 2007. **178**(3 Pt 1): p. 826-31; discussion 31-2.

121. Lee K, Tripathy D, Demark-Wahnefried W, Courneya KS, Sami N, Bernstein L, et al., Effect of Aerobic and Resistance Exercise Intervention on Cardiovascular Disease Risk in Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. *JAMA Oncol*, 2019. **5**(5): p. 710-4.

122. Lee K, Zhou J, Norris MK, Chow C, and Dieli-Conwright CM, Prehabilitative Exercise for the Enhancement of Physical, Psychosocial, and Biological Outcomes Among Patients Diagnosed with Cancer. *Curr Oncol Rep*, 2020. **22**(7): p. 71.

123. Leung PS, Aronson WJ, Ngo TH, Golding LA, and Barnard RJ, Exercise alters the IGF axis in vivo and increases p53 protein in prostate tumor cells in vitro. *J Appl Physiol (1985)*, 2004. **96**(2): p. 450-4.

124. Lewinsohn PM, Seeley JR, Roberts RE, and Allen NB, Center for epidemiologic studies depression scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychology and Aging*, 1997. **12**(2): p. 277-87.

125. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al., Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surg Endosc*, 2013. **27**(4): p. 1072-82.

126. Licker M, Karenovics W, Diaper J, Fresard I, Triponez F, Ellenberger C, et al., Short-Term Preoperative High-Intensity Interval Training in Patients Awaiting Lung Cancer Surgery: A Randomized Controlled Trial. *J Thorac Oncol*, 2017. **12**(2): p. 323-33.

127. Ligibel JA, Barry WT, Alfano C, Hershman DL, Irwin M, Neuhouser M, et al., Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early breast cancer (Alliance A011401): study design. *NPJ Breast Cancer*, 2017. **3**: p. 37.

128. Ligibel JA, Dillon D, Giobbie-Hurder A, McTiernan A, Frank E, Cornwell M, et al., Impact of a Pre-Operative Exercise Intervention on Breast Cancer Proliferation and Gene Expression: Results from the Pre-Operative Health and Body (PreHAB) Study. *Clin Cancer Res*, 2019. **25**(17): p. 5398-406.

129. Liu Y, Hu F, Li D, Wang F, Zhu L, Chen W, et al., Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *European urology*, 2011. **60**(5): p. 1029-44.

130. Loeb S, Carter HB, Schaeffer EM, Kettermann A, Ferrucci L, and Metter EJ, Distribution of PSA velocity by total PSA levels: data from the Baltimore Longitudinal Study of Aging. *Urology*, 2011. **77**(1): p. 143-7.

131. Loeb S, Curnyn C, Fagerlin A, Braithwaite RS, Schwartz MD, Lepor H, et al., Informational needs during active surveillance for prostate cancer: A qualitative study. *Patient Educ Couns*, 2018. **101**(2): p. 241-7.

132. Loprinzi PD and Kohli M. *Effect of physical activity and sedentary behavior on serum prostate-specific antigen concentrations: results from the National Health and Nutrition Examination Survey (NHANES), 2003-2006*. in *Mayo Clinic Proceedings*. 2013. Elsevier.

133. Loughney L and Grocott MP, Exercise and Nutrition Prehabilitation for the Evaluation of Risk and Therapeutic Potential in Cancer Patients: A Review. *Int Anesthesiol Clin*, 2016. **54**(4): p. e47-61.

134. Mahal BA, Butler S, Franco I, Spratt DE, Rebbeck TR, D'Amico AV, et al., Use of Active Surveillance or Watchful Waiting for Low-Risk Prostate Cancer and Management Trends Across Risk Groups in the United States, 2010-2015. *JAMA*, 2019. **321**(7): p. 704-6.

135. Mann S, Beedie C, and Jimenez A, Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. *Sports medicine (Auckland, N.Z.)*, 2014. **44**(2): p. 211-21.

136. Marzouk K, Assel M, Ehdaie B, and Vickers A, Long-Term Cancer Specific Anxiety in Men Undergoing Active Surveillance of Prostate Cancer: Findings from a Large Prospective Cohort. *J Urol*, 2018. **200**(6): p. 1250-5.

137. Matthes KL, Pestoni G, Korol D, Van Hemelrijck M, and Rohrmann S, The risk of prostate cancer mortality and cardiovascular mortality of nonmetastatic prostate cancer patients: A population-based retrospective cohort study. *Urol Oncol*, 2018. **36**(6): p. 309 e15- e23.

138. Matthew AG, Raz O, Currie KL, Louis AS, Jiang H, Davidson T, et al., Psychological distress and lifestyle disruption in low-risk prostate cancer patients: Comparison between active surveillance and radical prostatectomy. *J Psychosoc Oncol*, 2018. **36**(2): p. 159-74.

139. Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P, et al., Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery. *Surgery*, 2011. **150**(3): p. 505-14.

140. McCullough DJ, Nguyen LM, Siemann DW, and Behnke BJ, Effects of exercise training on tumor hypoxia and vascular function in the rodent preclinical orthotopic prostate cancer model. *J Appl Physiol (1985)*, 2013. **115**(12): p. 1846-54.

141. McInnis KJ and Balady GJ, Comparison of submaximal exercise responses using the Bruce vs modified Bruce protocols. *Med Sci Sports Exerc*, 1994. **26**(1): p. 103-7.

142. Meneses-Echávez JF, Correa-Bautista JE, González-Jiménez E, Schmidt Río-Valle J, Elkins MR, Lobelo F, et al., The Effect of Exercise Training on Mediators of Inflammation in Breast Cancer Survivors: A Systematic Review with Meta-analysis. *Cancer Epidemiology Biomarkers & Prevention*, 2016. **25**(7): p. 1009-17.

143. Menichetti J, Valdagni R, and Bellardita L, Quality of life in active surveillance and the associations with decision-making—a literature review. *Translational andrology and urology*, 2018. **7**(1): p. 160.

144. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC, et al., Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev*, 2012. **2012**(8): p. Cd007566.

145. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, and Topaloglu O, Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev*, 2012. **2012**(8): p. Cd008465.

146. Moholdt TT, Amundsen BH, Rustad LA, Wahba A, Lovo KT, Gullikstad LR, et al., Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *Am Heart J*, 2009. **158**(6): p. 1031-7.

147. Mugele H, Freitag N, Wilhelmi J, Yang Y, Cheng S, Bloch W, et al., High-intensity interval training in the therapy and aftercare of cancer patients: a systematic review with meta-analysis. *Journal of Cancer Survivorship*, 2019. **13**(2): p. 205-23.

148. Myers J, Prakash M, Froelicher V, Do D, Partington S, and Atwood JE, Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*, 2002. **346**(11): p. 793-801.

149. Nagarajan K, Bennett A, Agostini P, and Naidu B, Is preoperative physiotherapy/pulmonary rehabilitation beneficial in lung resection patients? *Interactive cardiovascular and thoracic surgery*, 2011. **13**(3): p. 300-2.

150. National Comprehensive Cancer Network (NCCN), *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer*. 2019.

151. National Comprehensive Cancer Network (NCCN), *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer*. 2017.

152. Neal D and Lilja H, Circulating Tumor Cell Count as an Indicator of Treatment Benefit in Advanced Prostate Cancer. *Eur Urol*, 2016. **70**(6): p. 993-4.

153. Neal DE, Metcalfe C, Donovan JL, Lane JA, Davis M, Young GJ, et al., Ten-year Mortality, Disease Progression, and Treatment-related Side Effects in Men with Localised Prostate Cancer from the ProtecT Randomised Controlled Trial According to Treatment Received. *European Urology*, 2020. **77**(3): p. 320-30.

154. Norris MK, Bell GJ, North S, and Courneya KS, Effects of resistance training frequency on physical functioning and quality of life in prostate cancer survivors: a pilot randomized controlled trial. *Prostate Cancer Prostatic Dis*, 2015. **18**(3): p. 281-7.

155. Norton L, Norton K, and Lewis N, Exercise training improves fasting glucose control. *Open access journal of sports medicine*, 2012. **3**: p. 209.

156. Nybo L, Sundstrup E, Jakobsen MD, Mohr M, Hornstrup T, Simonsen L, et al., High-intensity training versus traditional exercise interventions for promoting health. *Med Sci Sports Exerc*, 2010. **42**(10): p. 1951-8.

157. Oliveria SA, Kohl HW, 3rd, Trichopoulos D, and Blair SN, The association between cardiorespiratory fitness and prostate cancer. *Med Sci Sports Exerc*, 1996. **28**(1): p. 97-104.

158. Ornish D, Lin J, Chan JM, Epel E, Kemp C, Weidner G, et al., Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *Lancet Oncol*, 2013. **14**(11): p. 1112-20.

159. Ornish D, Lin J, Daubenmier J, Weidner G, Epel E, Kemp C, et al., Increased telomerase activity and comprehensive lifestyle changes: a pilot study. *Lancet Oncol*, 2008. **9**(11): p. 1048-57.

160. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al., Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*, 2005. **174**(3): p. 1065-9; discussion 9-70.

161. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al., Intensive lifestyle changes may affect the progression of prostate cancer. *The Journal of urology*, 2005. **174**(3): p. 1065-70.

162. Ornish DM, Lee KL, Fair WR, Pettengill EB, and Carroll PR, Dietary trial in prostate cancer: Early experience and implications for clinical trial design. *Urology*, 2001. **57**(4 Suppl 1): p. 200-1.

163. Orsini N, Bellocco R, Bottai M, Pagano M, Andersson SO, Johansson JE, et al., A prospective study of lifetime physical activity and prostate cancer incidence and mortality. *Br J Cancer*, 2009. **101**(11): p. 1932-8.

164. Osoba D, Rodrigues G, Myles J, Zee B, and Pater J, Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*, 1998. **16**(1): p. 139-44.

165. Papadopoulos E and Santa Mina D, Can we HIIT cancer if we attack inflammation? *Cancer Causes Control*, 2018. **29**(1): p. 7-11.

166. Park SW, Kim TN, Nam JK, Ha HK, Shin DG, Lee W, et al., Recovery of overall exercise ability, quality of life, and continence after 12-week combined exercise intervention in elderly patients who underwent radical prostatectomy: a randomized controlled study. *Urology*, 2012. **80**(2): p. 299-305.

167. Parker C, Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol*, 2004. **5**(2): p. 101-6.

168. Parker PA, Davis JW, Latini DM, Baum G, Wang X, Ward JF, et al., Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with favourable-risk prostate cancer undergoing active surveillance. *BJU Int*, 2016. **117**(3): p. 469-77.

169. Parsons JK, Pierce JP, Mohler J, Paskett E, Jung S-H, Humphrey P, et al., A randomized trial of diet in men with early stage prostate cancer on active surveillance: rationale and

design of the Men's Eating and Living (MEAL) Study (CALGB 70807 [Alliance]). *Contemporary clinical trials*, 2014. **38**(2): p. 198-203.

170. Parsons JK, Zahrieh D, Mohler JL, Paskett E, Hansel DE, Kibel AS, et al., Effect of a Behavioral Intervention to Increase Vegetable Consumption on Cancer Progression Among Men With Early-Stage Prostate Cancer: The MEAL Randomized Clinical Trial. *JAMA*, 2020. **323**(2): p. 140-8.

171. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al., Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. *Cell Metab*, 2016. **23**(3): p. 554-62.

172. Pehlivan E, Turna A, Gurses A, and Gurses HN, The effects of preoperative short-term intense physical therapy in lung cancer patients: a randomized controlled trial. *Ann Thorac Cardiovasc Surg*, 2011. **17**(5): p. 461-8.

173. Pierotti B, Altieri A, Talamini R, Montella M, Tavani A, Negri E, et al., Lifetime physical activity and prostate cancer risk. *Int J Cancer*, 2005. **114**(4): p. 639-42.

174. Poole DC and Gaesser GA, Response of ventilatory and lactate thresholds to continuous and interval training. *J Appl Physiol (1985)*, 1985. **58**(4): p. 1115-21.

175. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, and Coombes JS, The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. *Sports Med*, 2015. **45**(5): p. 679-92.

176. Regnaux JP, Lefevre-Colau MM, Trinquart L, Nguyen C, Boutron I, Brosseau L, et al., High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. *Cochrane Database of Systematic Reviews*, 2015(10).

177. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, and Chan JM, Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. *Cancer Res*, 2011. **71**(11): p. 3889-95.

178. Riihimäki M, Thomsen H, Brandt A, Sundquist J, and Hemminki K, What do prostate cancer patients die of? *The oncologist*, 2011. **16**(2): p. 175.

179. Rikli RE and Jones CJ, *Senior fitness test manual*. 2013: Human Kinetics.

180. Rosenberg M, Rosenberg self-esteem scale (RSE). *Acceptance and commitment therapy. Measures package*, 1965. **61**: p. 52.

181. Roth A, Nelson CJ, Rosenfeld B, Warshowski A, O'Shea N, Scher H, et al., Assessing anxiety in men with prostate cancer: further data on the reliability and validity of the Memorial Anxiety Scale for Prostate Cancer (MAX-PC). *Psychosomatics*, 2006. **47**(4): p. 340-7.

182. Roth AJ, Rosenfeld B, Kornblith AB, Gibson C, Scher HI, Curley-Smart T, et al., The memorial anxiety scale for prostate cancer: validation of a new scale to measure anxiety in men with with prostate cancer. *Cancer*, 2003. **97**(11): p. 2910-8.

183. Royston P, Multiple imputation of missing values. *Stata journal*, 2004. **4**(3): p. 227-41.

184. Ruiz-Casado A, Martin-Ruiz A, Perez LM, Provencio M, Fiuza-Luces C, and Lucia A, Exercise and the Hallmarks of Cancer. *Trends Cancer*, 2017. **3**(6): p. 423-41.

185. Rundqvist H, Augsten M, Stromberg A, Rullman E, Mijwel S, Kharaziha P, et al., Effect of acute exercise on prostate cancer cell growth. *PLoS One*, 2013. **8**(7): p. e67579.

186. Santa Mina D, Matthew AG, Hilton WJ, Au D, Awasthi R, Alibhai SM, et al., Prehabilitation for men undergoing radical prostatectomy: a multi-centre, pilot randomized controlled trial. *BMC Surg*, 2014. **14**(1): p. 89.

187. Sasso JP, Eves ND, Christensen JF, Koelwyn GJ, Scott J, and Jones LW, A framework for prescription in exercise-oncology research. *J Cachexia Sarcopenia Muscle*, 2015. **6**(2): p. 115-24.

188. Schluter K, Schneider J, Sprave T, Wiskemann J, and Rosenberger F, Feasibility of Two High-Intensity Interval Training Protocols in Cancer Survivors. *Med Sci Sports Exerc*, 2019. **51**(12): p. 2443-50.

189. Schmitt J, Lindner N, Reuss-Borst M, Holmberg HC, and Sperlich B, A 3-week multimodal intervention involving high-intensity interval training in female cancer survivors: a randomized controlled trial. *Physiol Rep*, 2016. **4**(3).

190. Schulz SVW, Laszlo R, Otto S, Prokopchuk D, Schumann U, Ebner F, et al., Feasibility and effects of a combined adjuvant high-intensity interval/strength training in breast cancer patients: a single-center pilot study. *Disabil Rehabil*, 2018. **40**(13): p. 1501-8.

191. Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS, et al., Efficacy of Exercise Therapy on Cardiorespiratory Fitness in Patients With Cancer: A Systematic Review and Meta-Analysis. *J Clin Oncol*, 2018. **36**(22): p. 2297-305.

192. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, et al., Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol*, 2003. **21**(9): p. 1653-9.

193. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al., Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*, 2009. **27**(3): p. 344-51.

194. Sekine Y, Chiyo M, Iwata T, Yasufuku K, Furukawa S, Amada Y, et al., Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. *Jpn J Thorac Cardiovasc Surg*, 2005. **53**(5): p. 237-43.

195. Shephard RJ and Shek PN, Effects of exercise and training on natural killer cell counts and cytolytic activity: a meta-analysis. *Sports Med*, 1999. **28**(3): p. 177-95.

196. Silver JK and Baima J, Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *American Journal of Physical Medicine & Rehabilitation*, 2013. **92**(8): p. 715-27.

197. Silver JK and Baima J, Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *Am J Phys Med Rehabil*, 2013. **92**(8): p. 715-27.

198. Silver JK. *Cancer prehabilitation and its role in improving health outcomes and reducing health care costs*. in *Seminars in oncology nursing*. 2015. Elsevier.

199. Simard S and Savard J, Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. *Support Care Cancer*, 2009. **17**(3): p. 241-51.

200. Simpson RJ, Bigley AB, Agha N, Hanley PJ, and Bollard CM, Mobilizing Immune Cells With Exercise for Cancer Immunotherapy. *Exerc Sport Sci Rev*, 2017. **45**(3): p. 163-72.

201. Singh F, Newton RU, Baker MK, Spry NA, Taaffe DR, and Galvao DA, Feasibility and Efficacy of Presurgical Exercise in Survivors of Rectal Cancer Scheduled to Receive Curative Resection. *Clin Colorectal Cancer*, 2017. **16**(4): p. 358-65.

202. Singh F, Newton RU, Baker MK, Spry NA, Taaffe DR, Thavaseelan J, et al., Feasibility of Presurgical Exercise in Men With Prostate Cancer Undergoing Prostatectomy. *Integr Cancer Ther*, 2017. **16**(3): p. 290-9.

203. Skolarus TA, Dunn RL, Sanda MG, Chang P, Greenfield TK, Litwin MS, et al., Minimally important difference for the Expanded Prostate Cancer Index Composite Short Form. *Urology*, 2015. **85**(1): p. 101-5.

204. Spielberger CD, *State-Trait anxiety inventory*. 2010: Wiley Online Library.

205. Stofan JR, DiPietro L, Davis D, Kohl 3rd H, and Blair SN, Physical activity patterns associated with cardiorespiratory fitness and reduced mortality: the Aerobics Center Longitudinal Study. *American journal of public health*, 1998. **88**(12): p. 1807-13.

206. Sweegers MG, Altenburg TM, Chinapaw MJ, Kalter J, Verdonck-de Leeuw IM, Courneya KS, et al., Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med*, 2018. **52**(8): p. 505-13.

207. Szymanski KM, Wei JT, Dunn RL, and Sanda MG, Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology*, 2010. **76**(5): p. 1245-50.

208. Talcott JA, Rieker P, Clark JA, Propert KJ, Weeks JC, Beard CJ, et al., Patient-reported symptoms after primary therapy for early prostate cancer: results of a prospective cohort study. *J Clin Oncol*, 1998. **16**(1): p. 275-83.

209. Tarle M, Kraljic I, and Kastelan M, Comparison between Nk Cell-Activity and Prostate-Cancer Stage and Grade in Untreated Patients - Correlation with Tumor-Markers and Hormonal Serotest Data. *Urological Research*, 1993. **21**(1): p. 17-21.

210. Toohey K, Pumpa K, McKune A, Cooke J, and Semple S, High-intensity exercise interventions in cancer survivors: a systematic review exploring the impact on health outcomes. *J Cancer Res Clin Oncol*, 2018. **144**(1): p. 1-12.

211. Toohey K, Pumpa KL, Arnolda L, Cooke J, Yip D, Craft PS, et al., A pilot study examining the effects of low-volume high-intensity interval training and continuous low to moderate intensity training on quality of life, functional capacity and cardiovascular risk factors in cancer survivors. *PeerJ*, 2016. **4**: p. e2613.

212. Twillie DA, Eisenberger MA, Carducci MA, Hseih W-S, Kim WY, and Simons JW, Interleukin-6: a candidate mediator of human prostate cancer morbidity. *Urology*, 1995. **45**(3): p. 542-9.

213. UEDA T, SADAR MD, SUZUKI H, AKAKURA K, SAKAMOTO S, SHIMBO M, et al., Interleukin-4 in patients with prostate cancer. *Anticancer research*, 2005. **25**(6C): p. 4595-8.

214. Uth J, Hornstrup T, Schmidt JF, Christensen JF, Frandsen C, Christensen KB, et al., Football training improves lean body mass in men with prostate cancer undergoing androgen deprivation therapy. *Scand J Med Sci Sports*, 2014. **24 Suppl 1**(S1): p. 105-12.

215. van de Wal M, van Oort I, Schouten J, Thewes B, Gielissen M, and Prins J, Fear of cancer recurrence in prostate cancer survivors. *Acta Oncol*, 2016. **55**(7): p. 821-7.

216. van den Bergh RC, Essink-Bot M-L, Roobol MJ, Schröder FH, Bangma CH, and Steyerberg EW, Do anxiety and distress increase during active surveillance for low risk prostate cancer? *The Journal of urology*, 2010. **183**(5): p. 1786-91.

217. van den Bergh RC, Korfage IJ, and Bangma CH, Psychological aspects of active surveillance. *Curr Opin Urol*, 2012. **22**(3): p. 237-42.

218. Van Hemelrijck M, Garmo H, Holmberg L, Ingelsson E, Bratt O, Bill-Axelson A, et al., Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. *J Clin Oncol*, 2010. **28**(21): p. 3448-56.

219. Vandersluis AD, Guy DE, Klotz LH, Fleshner NE, Kiss A, Parker C, et al., The role of lifestyle characteristics on prostate cancer progression in two active surveillance cohorts. *Prostate Cancer Prostatic Dis*, 2016. **19**(3): p. 305-10.

220. Vashistha V, Singh B, Kaur S, Prokop LJ, and Kaushik D, The Effects of Exercise on Fatigue, Quality of Life, and Psychological Function for Men with Prostate Cancer: Systematic Review and Meta-analyses. *Eur Urol Focus*, 2016. **2**(3): p. 284-95.

221. Vernooij RWM, Lancee M, Cleves A, Dahm P, Bangma CH, and Aben KKH, Radical prostatectomy versus deferred treatment for localised prostate cancer. *Cochrane Database of Systematic Reviews*, 2020(6).

222. Vickers AJ and Brewster SF, PSA Velocity and Doubling Time in Diagnosis and Prognosis of Prostate Cancer. *British journal of medical & surgical urology*, 2012. **5**(4): p. 162-8.

223. Waldhauer I and Steinle A, NK cells and cancer immunosurveillance. *Oncogene*, 2008. **27**(45): p. 5932-43.

224. Wallace M, Uncertainty and quality of life of older men who undergo watchful waiting for prostate cancer. *Oncology nursing forum*, 2002. **30**(2): p. 303-9.

225. Wallace M, Uncertainty and quality of life of older men who undergo watchful waiting for prostate cancer. *Oncol Nurs Forum*, 2003. **30**(2): p. 303-9.

226. Wang Y, Jin B, Paxton RJ, Yang W, Wang X, Jiao Y, et al., The effects of exercise on insulin, glucose, IGF-axis and CRP in cancer survivors: Meta-analysis and meta-regression of randomised controlled trials. *Eur J Cancer Care (Engl)*, 2020. **29**(1): p. e13186.

227. Warburton DE, Jamnik VK, Bredin SS, Burr J, Charlesworth S, Chilibeck P, et al., The 2011 Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and the Electronic Physical Activity Readiness Medical Examination (ePARmed-X+). *Heal Fit J Canada*, 2011. **4**: p. 24-5.

228. Warburton DE, McKenzie DC, Haykowsky MJ, Taylor A, Shoemaker P, Ignaszewski AP, et al., Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *Am J Cardiol*, 2005. **95**(9): p. 1080-4.

229. Weston KS, Wisloff U, and Coombes JS, High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med*, 2014. **48**(16): p. 1227-34.

230. Yanez B, Bustillo NE, Antoni MH, Lechner SC, Dahn J, Kava B, et al., The importance of perceived stress management skills for patients with prostate cancer in active surveillance. *Journal of behavioral medicine*, 2015. **38**(2): p. 214-23.

231. Yellen SB, Cella DF, Webster K, Blendowski C, and Kaplan E, Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*, 1997. **13**(2): p. 63-74.

APPENDIX A: PROSTATE CANCER TREATMENTS AND ACTIVE SURVEILLANCE

Prostate Cancer Treatments

Most prostate cancer patients undergo conventional treatments including surgery (radical prostatectomy), radiotherapy (e.g., external beam radiation therapy, brachytherapy, and systemic radiation therapy), or hormonal therapy (androgen deprivation therapy) [1]. Radical prostatectomy is the most common surgical procedure when there is no evidence of the prostate tumour spreading outside of the prostate gland. In this procedure, the prostate gland, often with some surrounding tissues (e.g., seminal vesicles), is resected [2]. There are two different approaches to radical prostatectomy in general: open approaches and laparoscopic approaches. Open approaches are considered a traditional way of treating prostate cancer where the prostate and adjacent tissues are removed through a single long incision. Two main operations are radical retropubic prostatectomy (through an incision made in the bowel abdomen, from the belly button to the pubic bone) and radical perineal prostatectomy (through an incision made between the anus and scrotum) [3, 4]. This approach is not used as often as in the past. On the other hand, laparoscopic approaches are more common for prostate cancer treatment in recent years [5]. Laparoscopic radical prostatectomy is an operation where the surgeon uses several smaller incisions and inserts long instruments to remove the prostate tumour [6]. Robotic prostatectomy is also a laparoscopic radical prostatectomy using a robotic interface (also known as the *da Vinci system*) and the surgeon controls robotic arms to operate while sitting at a control panel in the operating room [7]. Although the laparoscopic approaches seem to offer more precision and better manoeuvrability as well as less blood loss and pain, shorter hospital stay, and faster recovery than open radical surgeries, it profoundly depends on the surgeon's skill and experience similar to open approaches. Any type of prostate cancer surgery has side effects and the major

side effects include urinary incontinence, erectile dysfunction, loss of fertility, lymphedema, and inguinal hernia [8, 9].

Radiation therapy can be chosen as the first treatment when the cancer is low grade and the treatment is limited to the prostate gland or as a supplementary treatment when there is any sign of tumour residue/coming back/advance after surgery [10]. There are two types of radiation therapy: external beam radiation therapy (EBRT) and brachytherapy (also known as internal radiation therapy or seed implantation) [11]. EBRT used radiation beams targeting the prostate gland from outside of the body, and it is used to treat low-grade cancers or help alleviate certain prostate cancer-related symptoms (e.g., bone pain) [12]. To increase precision and reduce harm to adjacent healthy tissues, EBRT utilizes several techniques including three-dimensional conformal radiation therapy (3D-CRT) [13], intensity modulated radiation therapy (IMRT) [14], image-guided radiation therapy (IGRT) [15], volumetric modulated arc therapy (VMAT) [16], stereotactic body radiation therapy (SBRT) [17], and proton beam radiation therapy (PBRT) [18]. Although the procedure is quick and painless, there are some side effects from EBRT similar to prostatectomy such as bowel, urinary, and erection, problems as well as fatigue and lymphedema [19]. Alternatively, brachytherapy treats cancer using radioactive pellets, or "seeds", that are directly injected into the prostate. It is generally used to treat a low-grade tumour or sometimes high-risk cancer in combination with EBRT [20] and either low-dose rate (LDR) brachytherapy or high-dose rate (HDR) brachytherapy are used. There are several possible risks and side effects from brachytherapy including radiation precautions (e.g., infants and pregnant women) and travelling pellets for LDR brachytherapy [21] as well as any other sides effects from other prostate treatment such as bowel, urinary, or sexual problems [22].

Hormone therapy, also known as androgen deprivation therapy (ADT) or androgen suppression therapy is based on the idea that androgens (e.g., testosterone and dihydrotestosterone[DHT]) stimulate prostate tumour progression[23]. Hormonal therapy may be used in addition to radical prostatectomy or radiotherapy. It can be used when the prostate cancer has spread or if the patient is at a higher risk of cancer recurrence based on Gleason score or prostate cancer antigen (PSA) [24]. Types of hormone therapy include orchiectomy (surgical castration), luteinizing hormone-releasing hormone (LHRH) agonists (also called LHRH analogs or GnRH agonists), and other drugs such as LHRH antagonists, CYP17 inhibitors, anti-androgens, and estrogens [24]. Although side effects from hormone therapy depend on the type of drugs [25], common side effects may include sexual dysfunction [26], osteoporosis [27], muscle loss and weight gain[28], fatigue [29], and/or depression [30]. Hormone therapy has been widely used for prostate cancer treatment, however, further evidence is needed for several hormonal therapy-related issues such as treating early-stage cancer, early versus delayed treatment after surgery or radiation therapy [31], intermittent versus continuous hormone therapy [32], usage of combined/triple androgen blockade therapy [33], and castrate-resistant (low testosterone levels helped by other forms of hormone therapy, such as the drugs abiraterone and enzalutamide) versus hormone-refractory (no longer helped by any type of hormone therapy) prostate cancer [34, 35].

Chemotherapy has not been considered as a standard prostate cancer treatment before or after surgery, but it can be used if hormone therapy does not work when prostate cancer has spread out from the prostate gland [36]. Most common chemotherapy drugs for prostate cancer include Docetaxel (Taxotere), Cabazitaxel (Jevtana), Mitoxantrone (Novantrone), Estramustine (Emcyt). Although some drugs help men with prostate cancer increase survival [34, 37],

chemotherapy is still unlikely to cure prostate cancer [31]. Possible side effects of chemotherapy for prostate cancer include hair loss, nausea and vomiting, loss of appetite, diarrhea, and fatigue [38, 39].

Active Surveillance

In recent years, a clinical practice, “active surveillance”, has been introduced in low- or intermediate-risk prostate cancer patients [40]. Under active surveillance, prostate cancer patients are closely monitored using repeated prostate biopsies and serum prostate specific antigen (PSA) concentrations to determine whether there are any signs of tumour progression, but they do not receive any immediate treatment [41]. Therefore, active surveillance allows early-stage prostate cancer patients to avoid radical treatments, risks of tumour spreading during surgery, and side effects, as well as to maintain quality of life [42].

In a recent large cohort follow-up study with 82,429 men diagnosed with prostate cancer, there was no significant difference in prostate-cancer-specific mortality among surgery, radiotherapy, and active surveillance [43]. Furthermore, in the same cohort, general health-related or cancer-related quality of life, anxiety, and depression did not show significant differences among the three groups [44]. These results may imply that, without significant benefits in survival and patient-reported outcomes, traditional treatments such as prostatectomy or radiation therapy, which are accompanied by side effects, may not be preferable, while active surveillance might be a better option. Therefore, it can be expected that the number of early stage prostate cancer patients choosing active surveillance over radical treatments will continue to increase.

References

1. Cooperberg MR, Broering JM, and Carroll PR, Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol*, 2010. **28**(7): p. 1117-23.
2. Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, and Scardino PT, Cancer control with radical prostatectomy alone in 1,000 consecutive patients. *J Urol*, 2002. **167**(2 Pt 1): p. 528-34.
3. Frazier HA, Robertson JE, and Paulson DF, Radical prostatectomy: the pros and cons of the perineal versus retropubic approach. *J Urol*, 1992. **147**(3 Pt 2): p. 888-90.
4. Roehl KA, Han M, Ramos CG, Antenor JA, and Catalona WJ, Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. *J Urol*, 2004. **172**(3): p. 910-4.
5. Roumeguere T, Bollens R, Vanden Bossche M, Rochet D, Bialek D, Hoffman P, et al., Radical prostatectomy: a prospective comparison of oncological and functional results between open and laparoscopic approaches. *World journal of urology*, 2003. **20**(6): p. 360-6.
6. Guillonneau B and Vallancien G, Laparoscopic radical prostatectomy: the Montsouris technique. *J Urol*, 2000. **163**(6): p. 1643-9.
7. Binder J and Kramer W, Robotically-assisted laparoscopic radical prostatectomy. *BJU international*, 2001. **87**(4): p. 408-10.
8. Fowler FJ, Barry MJ, Lu-Yao G, Roman A, Wasson J, and Wennberg JE, Patient-re ported complications and follow-up treatment after radical prostatectomy: The national medicare experience: 1988–1990 (updated June 1993). *Urology*, 1993. **42**(6): p. 622-8.

9. Skolarus TA, Wolf AM, Erb NL, Brooks DD, Rivers BM, Underwood W, 3rd, et al., American Cancer Society prostate cancer survivorship care guidelines. *CA Cancer J Clin*, 2014. **64**(4): p. 225-49.

10. Cox JD, Gallagher MJ, Hammond EH, Kaplan RS, and Schellhammer PF, Consensus statements on radiation therapy of prostate cancer: guidelines for prostate re-biopsy after radiation and for radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *J Clin Oncol*, 1999. **17**(4): p. 1155.

11. Stein ME, Boehmer D, and Kuten A, *Radiation therapy in prostate cancer*, in *Prostate Cancer*. 2007, Springer. p. 179-99.

12. Fowler Jr FJ, Barry MJ, Lu-Yao G, Wasson JH, and Bin L, Outcomes of external-beam radiation therapy for prostate cancer: a study of Medicare beneficiaries in three surveillance, epidemiology, and end results areas. *Journal of Clinical Oncology*, 1996. **14**(8): p. 2258-65.

13. Zelefsky M, Leibel S, Gaudin P, Kutcher G, Fleshner N, Venkatramen E, et al., Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *International Journal of Radiation Oncology* Biology* Physics*, 1998. **41**(3): p. 491-500.

14. Zelefsky MJ, Fuks Z, Happersett L, Lee HJ, Ling CC, Burman CM, et al., Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. *Radiotherapy and Oncology*, 2000. **55**(3): p. 241-9.

15. Xing L, Thorndyke B, Schreibmann E, Yang Y, Li T-F, Kim G-Y, et al., Overview of image-guided radiation therapy. *Medical Dosimetry*, 2006. **31**(2): p. 91-112.

16. Zhang P, Happersett L, Hunt M, Jackson A, Zelefsky M, and Mageras G, Volumetric modulated arc therapy: planning and evaluation for prostate cancer cases. *International Journal of Radiation Oncology* Biology* Physics*, 2010. **76**(5): p. 1456-62.

17. King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al., Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol*, 2013. **109**(2): p. 217-21.

18. Konski A, Speier W, Hanlon A, Beck JR, and Pollack A, Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? *Journal of Clinical Oncology*, 2007. **25**(24): p. 3603-8.

19. Hamilton AS, Stanford JL, Gilliland FD, Albertsen PC, Stephenson RA, Hoffman RM, et al., Health outcomes after external-beam radiation therapy for clinically localized prostate cancer: results from the Prostate Cancer Outcomes Study. *J Clin Oncol*, 2001. **19**(9): p. 2517-26.

20. Yamada Y, Rogers L, Demanes DJ, Morton G, Prestidge BR, Pouliot J, et al., American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. *Brachytherapy*, 2012. **11**(1): p. 20-32.

21. Stone NN and Stock RG, Complications following permanent prostate brachytherapy. *Eur Urol*, 2002. **41**(4): p. 427-33.

22. Logghe P, Verlinde R, Bouttens F, Van den Broecke C, Deman N, Verboven K, et al., Long term outcome and side effects in patients receiving low-dose I125 brachytherapy: a retrospective analysis. *Int Braz J Urol*, 2016. **42**(5): p. 906-17.

23. Abrahamsson PA, Potential benefits of intermittent androgen suppression therapy in the treatment of prostate cancer: a systematic review of the literature. *Eur Urol*, 2010. **57**(1): p. 49-59.

24. Sharifi N, Gulley JL, and Dahut WL, Androgen deprivation therapy for prostate cancer. *JAMA*, 2005. **294**(2): p. 238-44.

25. Higano CS, Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. *Urology*, 2003. **61**(2): p. 32-8.

26. Basaria S, Lieb J, 2nd, Tang AM, DeWeese T, Carducci M, Eisenberger M, et al., Long-term effects of androgen deprivation therapy in prostate cancer patients. *Clin Endocrinol (Oxf)*, 2002. **56**(6): p. 779-86.

27. Daniell HW, Dunn SR, Ferguson DW, Lomas G, Niazi Z, and Stratte PT, Progressive osteoporosis during androgen deprivation therapy for prostate cancer. *J Urol*, 2000. **163**(1): p. 181-6.

28. Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, et al., Changes in body composition during androgen deprivation therapy for prostate cancer. *The Journal of Clinical Endocrinology & Metabolism*, 2002. **87**(2): p. 599-603.

29. Stone P, Hardy J, Huddart R, A'Hern R, and Richards M, Fatigue in patients with prostate cancer receiving hormone therapy. *Eur J Cancer*, 2000. **36**(9): p. 1134-41.

30. Pirl WF, Greer JA, Goode M, and Smith MR, Prospective study of depression and fatigue in men with advanced prostate cancer receiving hormone therapy. *Psychooncology*, 2008. **17**(2): p. 148-53.

31. Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al., EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Actas Urológicas Españolas (English Edition)*, 2011. **35**(10): p. 565-79.

32. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, et al., Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med*, 2013. **368**(14): p. 1314-25.

33. Akaza H, Hinotsu S, Usami M, Arai Y, Kanetake H, Naito S, et al., Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. *Cancer*, 2009. **115**(15): p. 3437-45.

34. De Bono J, Oudard S, Ozguroglu M, Hansen S, Machiels J, Shen L, et al., Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC). *Journal of Clinical Oncology*, 2010. **28**(15_suppl): p. 4508-.

35. Nanda A, Chen M-H, Moran BJ, Braccioforte MH, Dosoretz D, Salenius S, et al., Total Androgen Blockade Versus a Luteinizing Hormone–Releasing Hormone Agonist Alone in Men With High-Risk Prostate Cancer Treated With Radiotherapy. *International Journal of Radiation Oncology* Biology* Physics*, 2010. **76**(5): p. 1439-44.

36. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al., EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol*, 2011. **59**(1): p. 61-71.

37. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al., Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*, 2012. **367**(13): p. 1187-97.

38. Tipton JM, McDaniel RW, Barbour L, and Johnston MP, Putting evidence into practice: evidence-based interventions to prevent, manage, and treat chemotherapy-induced nausea and vomiting. *Clinical Journal of Oncology Nursing*, 2007. **11**(1): p. 69.

39. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al., Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med*, 2015. **373**(8): p. 737-46.

40. Parker C, Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol*, 2004. **5**(2): p. 101-6.

41. Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR, et al., Active surveillance for prostate cancer: a systematic review of the literature. *Eur Urol*, 2012. **62**(6): p. 976-83.

42. Cooperberg MR, Carroll PR, and Klotz L, Active surveillance for prostate cancer: progress and promise. *J Clin Oncol*, 2011. **29**(27): p. 3669-76.

43. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al., 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1415-24.

44. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al., Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med*, 2016. **375**(15): p. 1425-37.

APPENDIX B: INTERVENTION TRIALS DURING ACTIVE SURVEILLANCE

Lifestyle Interventions in Prostate Cancer Patients on Active Surveillance

There are a few lifestyle intervention trials that included an exercise component in prostate cancer patients undergoing active surveillance. One study investigated the effects of a year-long intense lifestyle program on prostate cancer progression and health-related quality of life (Prostate Cancer Lifestyle Trial, PCLT) [1, 2]. The intervention was comprised of a vegan diet, moderate-intensity aerobic exercise (walking 30 minutes per day for 6 days per week), stress management, and a weekly 1-hour support group session [3]. At 3 months, an interim analysis only for the experimental group showed significant improvements in cardiovascular risk factors such as body mass index, abdominal obesity, blood pressure, and lipid profile as well as several indicators of psychological functioning including mental component summary, intrusive thoughts, and avoidance [4]. Also, total and free PSA levels were not significantly improved although the percentage of free PSA showed a non-significant but clinically meaningful change (17.5±7.4 to 18.9±8.3 %; $p = 0.055$) [4]. Though preliminary, they further analyzed prostate gene expression and telomerase activity (Gene Expression Modulation by Intervention with Nutrition and Lifestyle, GEMINAL) where they found 48 up-regulated and 453 down-regulated transcripts relating to prostate tumorigenesis [5] and an increase in telomerase activity in peripheral blood mononuclear cells (2.0±0.4 to 2.2±0.5 ln; $p = 0.031$) implying telomere maintenance capacity in human immune-system cells [4]. After one year of intervention, in addition to similar improvements in cardiovascular risk factors, total PSA significantly reduced by 4% in the intervention group while it increased by 6% in the control group (-0.25±1.2 vs. 0.38±1.3 ng/ml, respectively; $p = 0.016$) [1]. Also, the growth of LNCaP prostate cancer cells (androgen-sensitive human prostate adenocarcinoma cells) was substantially inhibited by approximately 8-times in the intervention group compared to the control group (-69.94±19.5 vs. -9.06±42.8 %,

respectively; $p < 0.001$) [1]. Moreover, overall health-related quality of life increased in the intervention group compared to the control group ($p < 0.001$) although no significant differences were found in other subscales such as physical- and mental-health, perceived stress, and sexual function [2]. After 2 years of follow-up with clinical events since study entry, they reported that 2 of 43 (5%) patients in the intervention group and 13 of 49 (27%) patients in the control group had proceeded to invasive prostate cancer treatments (radical prostatectomy, radiotherapy, or hormone therapy; $p < 0.05$), while no significant differences in PSA levels and the number of other clinical events were found [6]. After 5 years of follow-up, telomere length increased in the intervention group and decreased in the control group ($p = 0.03$) while PSA and telomerase activity were not significantly different between groups ($p = 0.93$ and $p = 0.64$, respectively) [7].

Second, another randomized controlle trial with 26 men with prostate cancer undergoing active surveillance tested the effects of a six-month combined whole-grain diet and vigorous (60≤90% heart rate reserve [HRR] or % oxygen uptake reserve [VO_2R]) exercise program [8]. The exercise program included non-supervised aerobic exercise three times/week for 45 minutes/session targeting 70% of maximal heart rate in addition to at least 10,000 steps daily. The combined intervention resulted in an improvement of aerobic capacity (VO_{2peak}) in the intervention group (29±7 to 32±7 ml O_2/min/kg) compared to the control group (26±5 to 27±5 ml O_2/min/kg). No significant differences were found in body composition, cardiometabolic outcomes, and PSA after six months of intervention.

Last, one study with 40 overweight or obese men with PCa provided a presurgical weight loss intervention consisting of diet and physical activity [9]; however, only feasibility outcomes have been reported and the focus of the study is on men electing radical prostatectomy. Several other cohort, cross-sectional, and systematic review studies have also concluded that lifestyle

interventions are a promising avenue of research for improving tumor outcomes in PCa patients on AS [10-12].

Reference

1. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al., Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*, 2005. **174**(3): p. 1065-9; discussion 9-70.
2. Daubenmier JJ, Weidner G, Marlin R, Crutchfield L, Dunn-Emke S, Chi C, et al., Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance. *Urology*, 2006. **67**(1): p. 125-30.
3. Ornish DM, Lee KL, Fair WR, Pettengill EB, and Carroll PR, Dietary trial in prostate cancer: Early experience and implications for clinical trial design. *Urology*, 2001. **57**(4 Suppl 1): p. 200-1.
4. Ornish D, Lin J, Daubenmier J, Weidner G, Epel E, Kemp C, et al., Increased telomerase activity and comprehensive lifestyle changes: a pilot study. *Lancet Oncol*, 2008. **9**(11): p. 1048-57.
5. Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al., Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. *Proc Natl Acad Sci U S A*, 2008. **105**(24): p. 8369-74.
6. Frattaroli J, Weidner G, Dnistrian AM, Kemp C, Daubenmier JJ, Marlin RO, et al., Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology*, 2008. **72**(6): p. 1319-23.
7. Ornish D, Lin J, Chan JM, Epel E, Kemp C, Weidner G, et al., Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *Lancet Oncol*, 2013. **14**(11): p. 1112-20.

8. Eriksen AK, Hansen RD, Borre M, Larsen RG, Jensen JM, Overgaard K, et al., A lifestyle intervention among elderly men on active surveillance for non-aggressive prostate cancer: a randomised feasibility study with whole-grain rye and exercise. *Trials*, 2017. **18**(1): p. 20.

9. Demark-Wahnefried W, Nix JW, Hunter GR, Rais-Bahrami S, Desmond RA, Chacko B, et al., Feasibility outcomes of a presurgical randomized controlled trial exploring the impact of caloric restriction and increased physical activity versus a wait-list control on tumor characteristics and circulating biomarkers in men electing prostatectomy for prostate cancer. *BMC Cancer*, 2016. **16**(1): p. 61.

10. Kenfield SA, Chang ST, and Chan JM, Diet and lifestyle interventions in active surveillance patients with favorable-risk prostate cancer. *Curr Treat Options Oncol*, 2007. **8**(3): p. 173-96.

11. Burton AJ, Martin RM, Donovan JL, Lane JA, Davis M, Hamdy FC, et al., Associations of lifestyle factors and anthropometric measures with repeat PSA levels during active surveillance/monitoring. *Cancer Epidemiol Biomarkers Prev*, 2012. **21**(10): p. 1877-85.

12. Vandersluis AD, Guy DE, Klotz LH, Fleshner NE, Kiss A, Parker C, et al., The role of lifestyle characteristics on prostate cancer progression in two active surveillance cohorts. *Prostate Cancer Prostatic Dis*, 2016. **19**(3): p. 305-10.

APPENDIX C: PHYSICAL ACTIVITY, EXERCISE, AND PROSTATE CANCER

Physical Activity and Prostate Cancer

Over the last decade, many observational studies have examined the associations between physical activity and the risk of prostate cancer. A meta-analysis using 88,294 cases from 24 case-control and 19 cohort studies showed that a risk of prostate cancer was inversely associated with time spent in total physical activity (relative risk [RR] = 0.90; 95% confidence interval [CI] = 0.84-0.95; p=0.001), occupational physical activity (RR = 0.81; 95% CI = 0.75 to 0.91; p<0.001), and recreational physical activity (RR = 0.95; 95% CI = 0.89 to 1.00; p=0.07) [1]. Moreover, several high-quality studies from large national cohorts reported that there is a positive relationship between physical activity and prostate cancer survivorship [2-6]. For example, the results from the Health Professionals Follow-Up Study demonstrated that participating in vigorous physical activity three hours per week or more was associated with reduced prostate cancer-specific mortality by 46% and all-cause mortality by 61%. Interestingly, one study has reported an unfavorable association between a risk of prostate cancer and recreational physical activity (p =0.006 for trend) and household physical activity (p=0.04 for trend) [7], and another study has also showed an increased risk of prostate cancer in obese men (RR = 1.29; 95% CI = 1.00 to 1.66 for physical activity >1h/d vs. <1h/d). However, most of epidemiological studies support that an increased physical activity level reduces the risk and mortality of prostate cancer.

Exercise Interventions in Prostate Cancer Patients

A recent systematic review and meta-analysis involving 16 randomized controlled trials found that there were significant positive effects of exercise on cancer-specific fatigue (standardized mean difference [SMD] = 0.25; 95% CI = 0.02 to 0.49; p=0.03), sub-maximal

aerobic fitness (SMD = 0.49; 95% CI = 0.12 to 0.85; p=0.01), upper body strength (SMD = 0.26; 95% CI = 0.02 to 0.51; p=0.04), and lower body strength (SMD = 0.29; 95% CI = 0.07 to 0.50; p=0.01) [8]. There were statistically non-significant but meaning effects of exercise on VO_{2peak} (SMD = 0.27; 95% CI = 0.00 to 0.54; p=0.05) and sexual activity (SMD = 0.37; 95% CI = 0.00 to 0.73; p=0.05). Cancer-specific quality of life (SMD = 0.13; 95% CI = -0.08 to 0.34; p=0.23), PSA (SMD = 0.14; 95% CI = -0.06 to 0.35; p=0.17), systolic blood pressure (SMD = -0.10; 95% CI = -0.33 to 0.13; p=0.39) did not reach statistical significance; however, a sensitivity analysis for quality of life involving high-quality studies showed a significant improvement cancer-specific quality of life (SMD = 0.33; 95% CI = 0.08 to 0.58; p=0.009). According to the American College of Sport Medicine (ACSM) [9], the evidence of safety and efficacy of exercise training in prostate cancer patients is A-level (overwhelming data from randomized controlled trials) on safety, aerobic fitness, muscular strength, and fatigue and B-level (few randomized controlled trials exist, or they are small and the results are inconsistent) on quality of life, body composition, and physical function. Reported adverse events include soft-tissue injuries only (e.g., ankle sprain), which can be preventable using progressive and individualized exercise programming. The reasons for the heterogeneity of the findings from each study may include different exercise programs (resistance, aerobic, or resistance + aerobic), medical characteristics (metastasis), and/or treatment status (during radiotherapy or androgen deprivation therapy).

In summary, a body of evidence from RCTs showed that exercise can positively affect cancer-specific fatigue and quality of life, aerobic fitness and muscle strength in prostate cancer patients, while further evidence in cancer outcomes (e.g., PSA or survival) from large randomized controlled trials is needed to be established. In addition, none of exercise clinical

trials has focused on prostate cancer patients undergoing active surveillance, which also should be further investigated.

Reference

1. Liu Y, Hu F, Li D, Wang F, Zhu L, Chen W, et al., Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *European urology*, 2011. **60**(5): p. 1029-44.
2. Pierotti B, Altieri A, Talamini R, Montella M, Tavani A, Negri E, et al., Lifetime physical activity and prostate cancer risk. *Int J Cancer*, 2005. **114**(4): p. 639-42.
3. Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, and Elliott FG, Case-control study of lifetime total physical activity and prostate cancer risk. *Am J Epidemiol*, 2004. **159**(8): p. 740-9.
4. Giovannucci EL, Liu Y, Leitzmann MF, Stampfer MJ, and Willett WC, A prospective study of physical activity and incident and fatal prostate cancer. *Archives of internal medicine*, 2005. **165**(9): p. 1005-10.
5. Kenfield SA, Stampfer MJ, Giovannucci E, and Chan JM, Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol*, 2011. **29**(6): p. 726-32.
6. Johnsen NF, Tjonneland A, Thomsen BL, Christensen J, Loft S, Friedenreich C, et al., Physical activity and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Int J Cancer*, 2009. **125**(4): p. 902-8.
7. Wiklund F, Lageros YT, Chang E, Bälter K, Johansson J-E, Adami H-O, et al., Lifetime total physical activity and prostate cancer risk: a population-based case–control study in Sweden. *European journal of epidemiology*, 2008. **23**(11): p. 739-46.

8. Bourke L, Smith D, Steed L, Hooper R, Carter A, Catto J, et al., Exercise for Men with Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol*, 2016. **69**(4): p. 693-703.

9. Irwin M and Medicine ACoS, *ACSM's guide to exercise and cancer survivorship*. 2012: Human Kinetics.

APPENDIX D: ERASE TRIAL BASELINE QUESTIONNAIRE

Identification #: _____

Exercise During Active Surveillance for Prostate Cancer
The ERASE Trial

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Normand G. Boulé, PhD; Catherine J. Field, PhD; Kerry S. Courneya, PhD

BASELINE QUESTIONNAIRE

Instructions

Thank you for agreeing to participate in this study. In this questionnaire, we are going to ask you a series of questions about yourself. Many of the questions ask you about your physical and mental health, and some may be viewed as personal. It is important to answer as many of these questions as possible, however, if you feel uncomfortable answering certain questions please leave them blank. All responses are completely confidential and will never be used in any way that could link them to you. Many of the questions may seem similar but it is important to treat each question separately and provide an answer for each. There are no right or wrong answers and all we ask is that you provide responses that are as honest and accurate as possible. The questionnaire should take about 30-45 minutes of your time to complete.

If you have any questions about the questionnaire, please contact the study coordinator, Dong-Woo (Derek) Kang, at 780.492.8246 or derek.kang@ualberta.ca.

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	0	1	2	3
2. Do you have any trouble taking a long walk?	0	1	2	3
3. Do you have any trouble taking a short walk outside of the house?	0	1	2	3
4. Do you need to stay in bed or a chair during the day?	0	1	2	3
5. Do you need help with eating, dressing, washing yourself or using the toilet?	0	1	2	3

During the past week:	Not at all	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	0	1	2	3
7. Were you limited in pursuing your hobbies or other leisure time activities?	0	1	2	3
8. Were you short of breath?	0	1	2	3
9. Have you had pain?	0	1	2	3
10. Did you need to rest?	0	1	2	3
11. Have you had trouble sleeping?	0	1	2	3
12. Have you felt weak?	0	1	2	3
13. Have you lacked appetite?	0	1	2	3
14. Have you felt nauseated?	0	1	2	3
15. Have you vomited?	0	1	2	3
16. Have you been constipated?	0	1	2	3

During the past week:		Not at all	A little	Quite a bit	Very much
17.	Have you had diarrhea? ·····	0	1	2	3
18.	Were you tired? ·····	0	1	2	3
19.	Did pain interfere with your daily activities? ···	0	1	2	3
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television? ·····	0	1	2	3
21.	Did you feel tense? ·····	0	1	2	3
22.	Did you worry? ·····	0	1	2	3
23.	Did you feel irritable? ·····	0	1	2	3
24.	Did you feel depressed? ·····	0	1	2	3
25.	Have you had difficulty remembering things? ·	0	1	2	3
26.	Has your physical condition or medical treatment interfered with your <u>family</u> life? ·····	0	1	2	3
27.	Has your physical condition or medical treatment interfered with your <u>social</u> activities? ·····	0	1	2	3
28.	Has your physical condition or medical treatment caused you financial difficulties? ···	0	1	2	3

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall <u>health</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

The next questions are designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

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1. **Over the past 4 weeks**, how often have you leaked urine?

1	2	3	4	5
More than once a day	About once a day	More than once a week	About once a week	Rarely or never

2. Which of the following best describes your urinary control **during the last 4 weeks**?

1	2	3	4
No urinary control whatsoever	Frequent dribbling	Occasional dribbling	Total control

3. How many pads or adult diapers <u>per day</u> did you usually use to control leakage **during the last 4 weeks**?

0	1	2	3
None	1 pad per day	2 pads per day	3 or more pads per day

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

	No problem	Very small problem	Small problem	Moderate problem	Big problem
a. Dripping or leaking urine	0	1	2	3	4
b. Pain or burning on urination	0	1	2	3	4
c. Bleeding with urination	0	1	2	3	4
d. Weak urine stream or incomplete emptying	0	1	2	3	4
e. Need to urinate frequently during the day	0	1	2	3	4

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

1	2	3	4	5
No problem	Very small problem	Small problem	Moderate problem	Big problem

6. How big a problem, if any, has each of the following been for you?

	No problem	Very small problem	Small problem	Moderate problem	Big problem
a. Urgency to have a bowel movement ·····	0	1	2	3	4
b. Increased frequency of bowel movements ·····	0	1	2	3	4
c. Losing control of your stools ·····	0	1	2	3	4
d. Bloody stools ·····	0	1	2	3	4
e. Abdominal/ Pelvic/Rectal pain ·····	0	1	2	3	4

7. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

1	2	3	4	5
No problem	Very small problem	Small problem	Moderate problem	Big problem

8. How would you rate each of the following **during the last 4 weeks**?

	Very poor to none	Poor	Fair	Good	Very good
a. Your ability to have an erection? ·····	1	2	3	4	5
b. Your ability to reach orgasm (climax)? ·····	1	2	3	4	5

9. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

1	2	3	4
None at all.	Not firm enough for any sexual activity	Firm enough for masturbation and foreplay only	Firm enough for intercourse

10. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

1	2	3	4	5
I NEVER had an erection when I wanted one	I had an erection LESS THAN HALF the time I wanted one	I had an erection ABOUT HALF the time I wanted one	I had an erection MORE THAN HALF the time I wanted one	I had an erection WHENEVER I wanted one

11. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

1	2	3	4	5
Very poor	Poor	Fair	Good	Very good

12. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

1	2	3	4	5
No problem	Very small problem	Small problem	Moderate problem	Big problem

13. How would you rate each of the following **during the last 4 weeks**?

	No problem	Very small problem	Small problem	Moderate problem	Big problem
a. Hot flashes ·····	0	1	2	3	4
b. Breast tenderness/ enlargement ·····	0	1	2	3	4
c. Feeling depressed ·····	0	1	2	3	4
d. Lack of energy ·····	0	1	2	3	4
e. Change in body weight ··	0	1	2	3	4

The next questions are to better understand how patients cope with aspects of their prostate cancer and the medical tests frequently involved in their care.

I. Below is a list of comments made by men about prostate cancer. Please indicate by circling the number next to each item how frequently these comments were true for you **during the past week**.

		Not at all	Rarely	Some-times	Often
1.	Any reference to prostate cancer brought up strong feelings in me.	0	1	2	3
2.	Even though it's a good idea, I found that getting a PSA* test scared me.	0	1	2	3
3.	Whenever I heard about a friend or public figure with prostate cancer, I got more anxious about me having prostate cancer.	0	1	2	3
4.	When I thought about having a PSA* test, I got more anxious about me having prostate cancer.	0	1	2	3
5.	Other things kept making me think about prostate cancer.	0	1	2	3
6.	I felt kind of numb when I thought about prostate cancer.	0	1	2	3
7.	I thought about prostate cancer even though I didn't mean to.	0	1	2	3
8.	I had a lot of feelings about prostate cancer, but I didn't want to deal with them.	0	1	2	3
9.	I had more trouble falling asleep because I couldn't get thoughts of prostate cancer out of my mind.	0	1	2	3
10	I was afraid that the results from my PSA* test would show that my disease was getting worse.	0	1	2	3
11.	Just hearing the words "prostate cancer" scared me.	0	1	2	3

*PSA: prostate specific antigen

II. For the next three questions, please indicate how frequently these situations have **EVER** been true for you.

	Not at all	Rarely	Some-times	Often
12. I have been so anxious about my PSA* test that I have thought about delaying it. ·····	0	1	2	3
13. I have been so worried about my PSA* test result that I have thought about asking my doctor to repeat it. ·····	0	1	2	3
14. I have been so concerned about my PSA* test result that I have thought about having the test repeated at another lab to make sure they were accurate. ·····	0	1	2	3

III. Listed below are a number of statements concerning a person's beliefs about their own health. In thinking about **the past week**, please indicate how much you agree or disagree with each statement. Please circle the number of your answer.

	Strongly agree	Agree	Disagree	Strongly disagree
15. Because cancer is unpredictable, I feel I cannot plan for the future. ·····	0	1	2	3
16. My fear of having my cancer getting worse gets in the way of my enjoying life. ·····	0	1	2	3
17. I am afraid of my cancer getting worse. ·····	0	1	2	3
18. I am more nervous since I was diagnosed with prostate cancer. ·····	0	1	2	3

*PSA: prostate specific antigen

Most men who have been diagnosed with prostate cancer are worried, to varying degrees, that there might be a progression of the cancer. **By <u>progression</u>, we mean the possibility that the cancer could <u>grow</u> or <u>spread</u> to another part of the body.** The next questions are to better understand the experience of worries about cancer progression. Please read each statement and indicate to what degree it applied to you **DURING THE PAST MONTH** by circling the appropriate number.

---

0 Not at all	**1** A little	**2** Somewhat	**3** A lot	**4** A great deal

1.	I am worried or anxious about the possibility of cancer progression ·····	0	1	2	3	4
2.	I am afraid of cancer progression ·····	0	1	2	3	4
3.	I believe it is normal to be worried or anxious about the possibility of cancer progression ·····	0	1	2	3	4
4.	When I think about the possibility of cancer progression, this triggers other unpleasant thoughts or images (such as death, suffering, the consequences for my family) ·····	0	1	2	3	4
5.	I believe that I am fine and that the cancer will not progress ·····	0	1	2	3	4

6. In your opinion, are you at risk of having a cancer progression?

0 Not at all at risk	1 A little at risk	2 Somewhat at risk	3 A lot at risk	4 A great deal at risk

7. How often do you think about the possibility of cancer progression?

0 Never	1 A few times a month	2 A few times a week	3 A few times a day	4 Several times a day

8. How much time **<u>per day</u>** do you spend thinking about the possibility of cancer progression?

0 I don't think about it	1 A few seconds	2 A few minutes	3 A few hours	4 Several hours

9. How long have you been thinking about the possibility of cancer progression?

0 I don't think about it	1 A few weeks	2 A few months	3 A few years	4 Several years

Please read each statement and indicate to what degree it applied to you **DURING THE PAST MONTH** by circling the appropriate number.

1. How often have you thought about your chances of your cancer progressing?

1	2	3	4
Never	Sometimes	Often	Almost always

2. Have these thoughts affected your mood?

1	2	3	4
Never	Sometimes	Often	Almost always

3. Have these thoughts interfered with your ability to do daily activities?

1	2	3	4
Never	Sometimes	Often	Almost always

4. How concerned are you about the possibility of your cancer progressing one day?

1	2	3	4
Never	Sometimes	Often	Almost always

5. How often do you worry about your cancer progressing?

1	2	3	4
Never	Sometimes	Often	Almost always

6. How much of a problem is this worry?

1	2	3	4
Never	Sometimes	Often	Almost always

7. How often do you worry about the chance of family members developing cancer?

1	2	3	4
Never	Sometimes	Often	Almost always

8. How concerned are you about the possibility that you will ever need surgery or radiation therapy?

1	2	3	4
Never	Sometimes	Often	Almost always

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number that best indicates how you have felt during the past week. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that best describes how you felt.

During the PAST WEEK	Not at all	Some-what	Moderately so	Very much so
1. I felt calm ·····	1	2	3	4
2. I was tense ·····	1	2	3	4
3. I felt at ease ·····	1	2	3	4
4. I worried over possible misfortunes···	1	2	3	4
5. I felt frightened ·····	1	2	3	4
6. I felt self-confident ·····	1	2	3	4
7. I was jittery ·····	1	2	3	4
8. I was relaxed ·····	1	2	3	4
9. I was worried ·····	1	2	3	4
10 I felt steady ·····	1	2	3	4

Below is a list of statements concerning how you might have felt or behaved in the past week. Please use the following scale to indicate how often you felt or behaved in these ways in the past week.

During the PAST WEEK		Rarely or none (<1 day)	Some of the time (1-2 days)	Much of the time (3-4 days)	Most or all of the time (5-7 days)
1.	I felt depressed	0	1	2	3
2.	I felt that everything I did was an effort	0	1	2	3
3.	My sleep was restless	0	1	2	3
4.	I was happy	0	1	2	3
5.	I felt lonely	0	1	2	3
6.	People were unfriendly	0	1	2	3
7.	I enjoyed life	0	1	2	3
8.	I felt sad	0	1	2	3
9.	I felt that people disliked me	0	1	2	3
10	I could not get "going"	0	1	2	3

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past week.

During the PAST WEEK		Not at all	A little bit	Some-what	Quite a bit	Very much
1.	I feel fatigued ·····	0	1	2	3	4
2.	I feel weak all over ·····	0	1	2	3	4
3.	I feel listless ("washed out")·····	0	1	2	3	4
4.	I feel tired ·····	0	1	2	3	4
5.	I have trouble starting things because I am tired·····	0	1	2	3	4
6.	I have trouble finishing things because I am tired·····	0	1	2	3	4
7.	I have energy ·····	0	1	2	3	4
8.	I am able to do my usual activities ·····	0	1	2	3	4
9.	I need to sleep during the day·····	0	1	2	3	4
10	I am too tired to eat ·····	0	1	2	3	4
11.	I need help doing my usual activities·····	0	1	2	3	4
12.	I am frustrated by being too tired to do the things I want to do·····	0	1	2	3	4
13.	I have to limit my social activity because I am tired·····	0	1	2	3	4

The next questions ask you about your feelings and thoughts during the last month. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each one fairly quickly. For each question, please choose from the following alternatives:

In the <u>LAST MONTH</u>, how often have you…	Never	Almost never	Some-times	Fairly often	Very often
1. been upset because of something that happened unexpectedly ……	0	1	2	3	4
2. felt that you were unable to control the important things in your life ……	0	1	2	3	4
3. felt nervous and stressed……	0	1	2	3	4
4. dealt successfully with irritating life hassles ……	0	1	2	3	4
5. felt that you were effectively coping with important changes that were occurring in your life……	0	1	2	3	4
6. felt confident about your ability to handle your personal problems……	0	1	2	3	4
7. felt that things were going your way ……	0	1	2	3	4
8. found that you could not cope with all the things that you had to do ……	0	1	2	3	4
9. been able to control irritations in your life	0	1	2	3	4
10 felt that you were on top of things……	0	1	2	3	4
11. been angered because of things that happened that were outside of your control ……	0	1	2	3	4
12. found yourself thinking about things that you have to accomplish……	0	1	2	3	4
13. been able to control the way you spend your time ……	0	1	2	3	4
14. felt difficulties were piling up so high that you could not overcome them……	0	1	2	3	4

The next questions concern the general perceptions that you currently have about yourself. Please circle the number that best reflects your current view of yourself using the following scale as a guide for your responses.

		Strongly Disagree	Disagree	Agree	Strongly Agree
1.	On the whole I am satisfied with myself. ··	1	2	3	4
2.	At times I think that I am no good at all ····	1	2	3	4
3.	I feel that I have a number of good qualities ·····	1	2	3	4
4.	I am able to do things as well as most other people·····	1	2	3	4
5.	I feel I do not have much to be proud of···	1	2	3	4
6.	I certainly feel useless at times ·····	1	2	3	4
7.	I feel that I am a person of worth, at least on an equal plane with others ·····	1	2	3	4
8.	I wish I could have more respect for myself·····	1	2	3	4
9.	All in all, I am inclined to feel that I am a failure ·····	1	2	3	4
10	I take a positive attitude toward myself ····	1	2	3	4

For this next question, we would like you to recall the amount of exercise you have done during the past month.

When answering these questions please:

- Only count exercise sessions that lasted 10 minutes or longer in duration.
- Only count exercise that was done during free time (i.e., not occupation or housework).
- Note that the main difference between the first three categories is the intensity of the endurance (aerobic) exercise and the fourth category is for strength (resistance) exercise.
- Write the average frequency on the first line and the average duration on the second.
- Write in "0" if you did not do any exercise in one of the categories.

Considering a typical week (7 days) over the **PAST MONTH**, how many times on the average did you do the following kinds of exercise?

AEROBIC EXERCISE	Times Per Week	Average Duration Per Session
a. VIGOROUS EXERCISE = *HEART BEATS RAPIDLY, SWEATING* (e.g., running, aerobics classes, cross country skiing, vigorous swimming, vigorous bicycling)	times/week	minutes/time
b. MODERATE EXERCISE = *NOT EXHAUSTING, LIGHT PERSPIRATION* (e.g., fast walking, tennis, easy bicycling, easy swimming, popular or folk dancing)	times/week	minutes/time
c. LIGHT EXERCISE = *MINIMAL EFFORT, NO PERSPIRATION* (e.g., easy walking, yoga, bowling, shuffleboard)	times/week	minutes/time
RESISTANCE/STRENGTH EXERCISE (e.g., weight lifting, push-ups, sit-ups, resistance band)	times/week	minutes/time

The following questions ask you to rate how you feel about **doing a high-intensity aerobic interval exercise training (HIIT) program** during active surveillance for your prostate cancer. Please pay careful attention to the words and descriptions for each scale and circle the number that best represents how you feel.

The HIIT exercise program involves 2-minutes of high-intensity walking or running on a treadmill (about 85-100% of maximal intensity) directly followed by 2-minutes of light walking recovery, repeated 5-8 times. One exercise session lasts approximately 30-40 minutes including warm-up and cool-down. It will be performed 3 days per week for 12 weeks at our fitness center at the University of Alberta.

---

1. How beneficial do you think it will be for you to do this HIIT program during active surveillance for your prostate cancer?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

2. How enjoyable do you think it will be for you to do this HIIT program during active surveillance for your prostate cancer?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

3. How supportive do you think family/friends will be of you doing this HIIT program during active surveillance for your prostate cancer?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

4. How motivated are you to do this HIIT program during active surveillance for your prostate cancer?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

5. How difficult do you think it will be for you to do this HIIT program during active surveillance for your prostate cancer?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

6. How much control do you think you will have over doing this HIIT program during active surveillance for your prostate cancer?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

7. How confident are you that you will be able to do this HIIT program during active surveillance for your prostate cancer?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

The next questions ask you about any possible benefits or harms of doing the high-intensity aerobic interval exercise training (HIIT) program during active surveillance for your prostate cancer. Please use the scales below to guide your responses.

-3	-2	-1	0	1	2	3
Very much worse	Somewhat worse	Slightly worse	No change	Slightly better	Somewhat better	Very much better

What effect, if any, do you think the HIIT exercise program will have on each of the following for you?

1.	Your physical fitness	-3 (worse)	-2	-1	0	1	2	3 (better)
2.	Your ability to stop thinking about your prostate cancer	-3 (worse)	-2	-1	0	1	2	3 (better)
3.	Your sense of control over your prostate cancer	-3 (worse)	-2	-1	0	1	2	3 (better)
4.	Your preparation for prostate cancer treatments if they are needed	-3 (worse)	-2	-1	0	1	2	3 (better)
5.	Your fear and worry of your prostate cancer progressing	-3 (worse)	-2	-1	0	1	2	3 (better)
6.	The chance that you will need prostate cancer treatments	-3 (higher)	-2	-1	0	1	2	3 (lower)
7.	Your quality of life	-3 (worse)	-2	-1	0	1	2	3 (better)
8.	Your immune system's ability to fight your cancer	-3 (worse)	-2	-1	0	1	2	3 (better)
9.	The growth of your prostate cancer	-3 (worse)	-2	-1	0	1	2	3 (better)
10.	The aggressiveness of the biology (grade) of your prostate cancer	-3 (worse)	-2	-1	0	1	2	3 (better)
11.	Your PSA levels	-3 (higher)	-2	-1	0	1	2	3 (lower)
12.	How long you survive	-3 (worse)	-2	-1	0	1	2	3 (better)

Any other positive or negative effects you expect?

_____

This part of the questionnaire is needed to help understand the characteristics of the people participating in the study. For this reason, it is very important information. All information is held in strict confidence and its presentation to the public will be group data only.

---

1. Age: _____

2. Current Marital Status:

Never Married	☐	Married	☐	Common Law	☐
Separated	☐	Widowed	☐	Divorced	☐

3. Education (Please check highest level attained):

Some High School	☐	Completed High School	☐
Some University/College	☐	Completed University/College	☐
Some Graduate School	☐	Completed Graduate School	☐

4. Annual Family Income:

< 20,000	☐	20,000 – 39,999	☐
40,000 – 59,999	☐	60,000 – 79,999	☐
80,000 – 99,999	☐	> 100,000	☐

5. Current Employment Status:

Full Time	☐	Part Time	☐	Sick Leave	☐
Retired	☐	Homemaker	☐	Disability	☐

6. What is your primary ethnic origin or race?

White	☐	Black	☐	Hispanic	☐
Asian	☐	Aboriginal	☐	Other	_____

7. Which of the following best describes your current smoking status?

Never Smoked	☐	Ex-Smoker	☐	Current Smoker	☐

8. Which of the following best describes your current alcohol consumption?

Never Drink	☐	Social Drinker	☐	Regular Drinker (drink every day)	☐

9. In the past month, was your ability to exercise limited by any health condition, injury, or disability?

1	2	3	4	5
No, Not at All	A Little	Somewhat	Quite A Lot	Completely

If yes, what is it? _____

10. Are you currently taking any medications or supplements?
(e.g., blood pressure, anxiety, pain, insomnia, vitamins, prostate supplements, etc.).

Medication or Supplement (e.g., Tenormin) (e.g., Super Prostate)	Purpose (e.g., Hypertension) (e.g., Prostate health)	Dose (if known) (e.g., 50mg twice per day) (e.g., 1 tablet per day)

Participant initials: _____

Questionnaire completion date: __ __ __ __ - __ __ - __ __
y y y y - m m - d d

Please feel free to make any comments concerning your prostate cancer, active surveillance, the questionnaire, the exercise study, or anything else you think may be helpful to us.

Thank you very much for your participation in this research project. Please place the completed questionnaire in the envelope provided and bring it to your scheduled fitness test.

APPENDIX E: ERASE TRIAL ASSESSMENT PROTOCOL

ERASE Trial Assessment Protocol

I. Blood Draw

a. Paperwork

- Fill out a DynaLife requisition form (gray-color).
  *required info: Participant's PHN, Sex, Last name, First name, Date of birth, and Fasting hours
- Fill out a research blood draw requisition form (red-color) and highlight the contact person and number in the sheet.
- Fill out six blood tube labels (required info: Participant number and Date of blood draw) and put two 6mL EDTA (purple top) blood vials in a plastic biohazard bag with "Refrigerate" checked.
  *use a permanent marker on the labels.

b. Instructions for Participants

> Please abstain from any food and beverages other than water at least 12 hours prior to your scheduled time.
>
> If you are on any medications, take them on your usual schedule and complete the medication question in the questionnaire.
>
> Please bring a light breakfast that you can have after the blood draw and before fitness testing.
>
> Refrain from smoking, consuming alcohol and caffeine at least 3 hours before testing.
>
> Avoid strenuous physical activity one day (24 hours) prior to testing.

c. Blood work

- Meet the participant in the waiting area at Level 0 of the Kaye Edmonton Clinic at the scheduled time.
- Fill out the blood collection form.
- Pull out the ticket number out and wait for the number called out from a nurse (this is just for the staff checking in and submitting documents).
- Go to the registration desk and submit:
  - Dyna-Life requisition (gray-color)
  - Research blood requisition (red-color) – emphasize the highlighted section ("call Dhruvesh after collection for pick-up")
  - Blood vials in the plastic bag.
- Come back to the patient and wait them to call out the number again.
- Once called out, let the patient follow the nurse next to the front desk.
- Text the second tester for a heads up.
- Once blood draw is done, escort him to the fitness testing room.

II. Body Composition

a. Weight and Height

- Purpose
  - To calculate Body Mass Index (BMI) as a measure of body composition.
  - Weight is also used to calculate the relative VO_{2peak} from the absolute term.
- Equipment
  - Electronic body weight scale located in the RTF testing room.
  - SECA movable stadiometer with 'squaring' at top at the wall.
- Procedure
  - Have participant wearing minimal clothing and having empty pockets with shoes removed
  - Have participant step onto the stadiometer with their back to the wall and heels flat against the floor and back panel
  - Have them look straight ahead, as tall as possible and take a deep breath while the measurement is taken
  - Record weight and height to the nearest 0.1kg
  - Record height to the nearest 0.1cm

b. Waist and Hip Circumferences

- Purpose
  - To quantify and estimate body fat distribution
- Equipment
  - A flexible yet inelastic tape measure
- Procedure
  - The tape should be placed on the skin surface without compressing the subcutaneous adipose tissue.
  - Take duplicate measures at each site and retest if duplicate measurements are not within 5mm.
  - Repeat measures should be done after allowing time for skin to regain normal t e x t u r e .
  - For waist circumference, with the subject standing, arms at the sides, feet together, and abdomen relaxed, horizontal measure is taken directly above the iliac crest.
  - For hip circumference, With the subject standing and feet together, a horizontal measure is taken at the maximal circumference of the buttocks.

III. Physical Fitness/Function Test

a. Cardiopulmonary Fitness Test

- Purpose
  - To assess cardiopulmonary fitness by measuring peak oxygen consumption during maximal exercise
- Equipment
  - Woodway treadmill (up to 20% and 10mph)
  - Parvo-Medics True One R2400 Metabolic Measurement Cart - Flow and gas calibrated before every test, signal display before and after each test (see Pretest Setup in protocol)
  - Hans Rudolph Calibration Syringe
  - Polar heart rate monitors
  - Welch-Allyn Blood Pressure Cuff
  - Stethoscope
  - Vacumetics C201 Pulse Oximeter
- Procedure

<u>Gas Calibration</u>

- Find and press Gas Calibration on the main home screen
- Ensure the temperature, pressure, and humidity match our weather station, correct them if necessary. Push ok
- Turn on gas tank and ensure it is at 3 psi (computer will prompt this as well)
- The system will automatically sample room air and standard air
- If the change in Gain Factor is <1%, press save. If it is > 1.0% press cancel and calibrate again.
- If on the 3rd calibration, the Gain factor is still >1.0%, save the calibration and recalibrate against that calibration (total of 4 calibrations)
  * Note - if Gain Factor is >3% check that the cart is set up correctly and there are no leaks as 3% would indicate something going wrong

<u>Flow Calibration</u>

- Find and press Flow Calibration on the main home screen
- Ensure the temperature, pressure, and humidity match our weather station, correct them if necessary. Push ok
- Attach the Hans Rudolph calibration syringe to the mouthpiece on the calibration tube
- The flow calibration is divided into 3 stages requiring calibration strokes:
  - Detection (1) - to ensure the strokes are being read properly
  - Flushes (4) - to flush the accumulated hot air inside the heated pneumolachometer out
  - Strokes (5) - to measure the volume of flow at different flow rates, from slow to maximal expiration
    - Using the lines on screen, pump the syringe so that it stays within each zone allowing the zones to disappear

    - Pressing the Cancel button will cancel the last stroke in case the syringe got stuck
    - Pressing Baseline will re-sample baseline if you suspect it has drifted
- When the calibration strokes are finished, the program will calculate new flowmeter volumes in the save data screen.
- If the Diff: is less than <1.0%, press save. If the Diff: is >l.0% press cancel and calibrate again
- If on the 3rd calibration, the Diff : is still >1.0%, save the calibration and recalibrate against that calibration (total of 4 calibrations)
  * Note - if Diff: is >3% check that the cart is set up correctly and there are no leaks as 3% would indicate something going wrong

Pre-Test Signal Display

- Find and press Signal Display on the main home screen.
- Click the check boxes for "0" and "1".
- Watching the values for O_2 and CO_2, wait for the numbers to stabilize (1 - 20 seconds) and record the values on the backside of the treadmill testing sheet.

Treadmill Test – Warm-up and gear up

- Ask if participant want go to the bathroom (recommended to go)
- Explain test to participant making sure to hit key points from the Modified Bruce Protocol Script (Appendix)
- Warm up takes place at a walking speed for 5 minutes before the actual graded exercise test (GXT), 0-2.5min at 1.7mph and 2.5-5.0min at 2.5mph
- Between the 4th and 5th minute HR, BP and SaO_2 are measured
- Immediately following the end of the warm up, go over stop protocol (hand in the middle of the front treadmill bar) so that it is the last thing in the participant's mind before the test starts.
- Allow the participant a 5 minute break to drink water and get setup with the headgear and mouthpiece.
- Once the participant is setup with the headgear and mouthpiece, have them step onto the treadmill facing forward and attach the hose from the cart to their mouthpiece.
- Start the test on the cart while the participant is standing.
- Wait for the O_2 concentration to get to <18.5% and push OK.
- Have the participant remain standing until the first set of metabolic measurements comes up (~ 15 seconds).
    - If RER ≤ 1.00, take the participants standing HR, BP and SaO_2 then start the test at the 1-minute mark.
    - If RER ≥ l.00, have the participant continue to stand another minute, take standing HR, BP and SaO_2, and start the test at the 2-minute mark.

  * Test should only start at the 1 or 2 minute marks, not at½ or¼ intervals

Treadmill Test (Modified Bruce Protocol; McINNIS K & Balady GJ, 1994)

- The test will be terminated at any stage if contraindications to graded exercise occur:
  - Angina or angina like symptoms
  - Drop in SBP > 10mmHg despite increased workload
  - Excessive rise in SBP > 250mmHg and/or DBP > 115mmHg
  - Shortness of Breath, wheezing, leg cramps or claudication
  - Light headedness, confusion, ataxia, pallor, cyanosis, nausea/cold clammy skin
  - Failure of HR to increase with increased workload
  - Noticeable changes in heart rhythm
  - SaO_2 of less than 90%
- Once the test has started, follow the workload increases according to the treadmill testing sheet, filling in HR, BP, SaO_2 and RPE where noted
- The participant goes until they feel that they can no longer exercise or keep up with the workload required and indicates stopping using the previously discussed stop protocol. Stop the treadmill belt immediately but have the participant continue to step on the spot while taking maximal HR, BP and SaO_2 measurements.
- Once the VO_2 measurements on the computer begin to drop (~15sec), press "Stop Test" on the computer and remove the mouthpiece/headgear from the participant.
- Allow the participant to have a couple drinks of water then immediately start them on the cool down

* Important Notes
  - Throughout test participants should be verbally encouraged.
  - Ensure participant does not hold onto the treadmill tightly during test (tight
    enough to reduce workload), while light grip for balance is acceptable.
  - NEVER change the spit trap in the final minute of a stage or right at the end of
    the test. The metabolic readings during these periods of time are crucial and should not be disrupted.

Protocol – Cool-down

- Follow the 5-minute cool down workloads according to the treadmill testing sheet.
- Ask participant their end RPE and reason for stopping the test.
- After the initial 1-minute, take HR, BP, and SaO_2 measurements.
- Once the 5-minute cool down has finished, have the participant step off the treadmill, sit down and rest for an additional 5 minute.

- Take HR and BP one more time to ensure it is safe for them to move on the next tests: BP back to pre exercise values and HR<l00bpm.

Protocol – Reports

- Perform another signal display. If the values differ from the initial ones by >0.05, circle "Yes" on the sheet and then a drift will be calculated on the final VO_2 values.
- Print/Save the following metabolic results under text report.
  - Click "Text Report" → "Config" → choose "15 Seconds" → "Ok" → print →
  - Click "Excel Export" → save in USB as "ERASE00BL(or FU)" (e,g, ERASE06FU)
  - Click "Ventilatory Threshold" button → pick a VT (see VT Appendix for details on picking a VT) → print
  - Find FPO number from top right corner beside the part1c1pant's name → click Start button on the Windows and go to "FPO shortcut" folder → copy the participant's FPO file and paste it in USB without renaming.

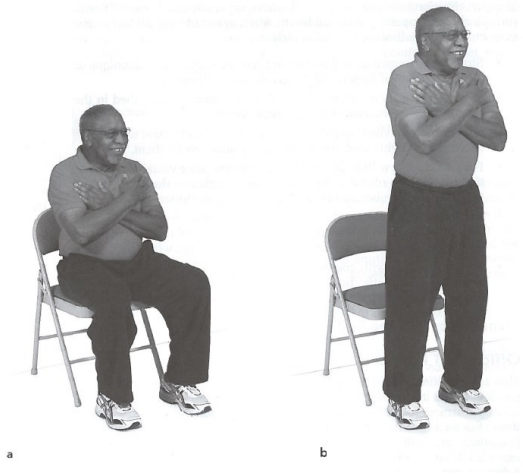
b. Physical Functioning Test (Senior's Fitness Test; Senior Fitness Test Manual-2nd Edition, Human Kinetics, 2013)

1) 30-second Chair Stand Test

- Purpose
  - To assess lower-body strength
- Equipment
  - Stopwatch; Straight-back chair with a seat height of approximately 17 inches (placed against a wall to prevent slipping)
- Procedure
  - Instruct participant to sit in the middle of the chair with back straight, feet flat on the floor, and arms crossed at the wrists and held against the chest (a).
  - On the signal "go", the participant rises to a full stand, then returns to a fully seated position (b).
  - Before testing, have the participant practice one or two stands.
  - Demonstrate the test slowly to show proper form, then a faster pace that the objective is to do the best on can within safety limits.
  - Encourage the participant to complete as many full stands as possible in the 30 seconds.
  - Administer only on trial.
  - The test time can stop once you observe the person is no longer able to perform additional stands.

- The score is the total number of stands completed in 30 seconds. If a person is more than halfway up at the end of 30 seconds, it counts as a full stand.

• Important Notes



  - Count the number out loud that participant can listen. If participant did not follow the instructed posture (cheating), do not count the ones participant did not do properly and let participant know immediately.
  - Ask if participant have any joint issues, especially knee, and inform that they can stop at any time if any issue occurs (e.g., serious knee pain and dizziness).
  - Ensure that the chair is not slipping (even can have someone hold it steady).
  - Watch that the chair is under the participants when they sit, especially for people who are visually impaired or physically and cognitively frail.
  - Watch for balance problems; quick movement could especially increase instability for people with sensory impairments (e.g., vision or inner ear problems).

<u>2) 30-second Arm Curl Test</u>

• Purpose
  - To assess upper-body strength

• Equipment
  - Stopwatch; Straight-back chair with no arms; 5-pound (for women) and 8-pound (for men) dumbbells

• Procedure
  - Have the participant sit on a chair with back straight and feet flat on the floor, with the dominant side of the body close to the edge of the seat.
  - The weight is held down at the side, perpendicular to the floor, in the dominant hand with a handshake grip.
  - From the down position, as the elbow bends the weight is curled up, with the palm gradually rotating to a facing-up position during flexion of the elbow.
  - The weight is returned as the elbow is fully extended down, with the hand returning to a handshake grip.
  - The wrist should not move-the bending is at the elbow.
  - Demonstrate the test slowly to illustrate the form, then at a faster speed to illustrate the pace.

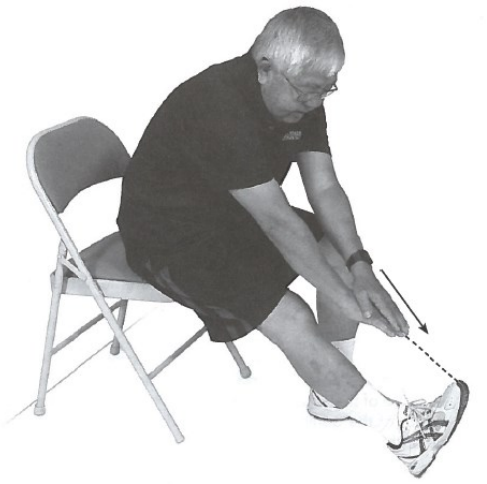
- Have the participant practice one or two repetitions without the weight to ensure proper form.
- On the signal "go," the participant curls the weight through the full range of motion (from full extension to full flexion of the lower arm) as many times as possible in 30 seconds.
- The upper arm must remain still throughout the test. If needed, brace the elbow against the body helps stabilize the upper arm.
- The score is the total number of arm curls executed in 30 seconds. If the arm is more than halfway up at the end of 30 seconds, it counts as a curl.
- Administer only one trial.

- Important Notes
  - Count the number out loud that participant can listen. If participant did not follow the instructed posture (cheating), do not count the ones participant did not do properly and let participant know immediately.
  - If participant did not follow the instructed posture (cheating), do not count the ones participant did not do properly
  - Make sure participants do not have extensive flexion at the wrist when performing the test. The flexion and extension are from the elbow-not the wrist. The wrist should not bend forward and backward.
  - Ask participants if they have any elbow, wrist, or hand pain.

<u>3) Chair Sit-and-Reach Test</u>

- Purpose
  - To assess lower-body {primarily hamstring) flexibility
- Equipment
  - 18-inch ruler; Chair with a seat height of 17 inches chair (placed against a wall to prevent slipping)
- Procedure

- The participant sits on the edge of the chair.
- The crease between the top of the leg and the buttocks should be even with the front edge of the chair seat.
- One leg is bent and slightly off to one side with the foot flat on the floor.
- The other leg is extended as straight as possible in front of the hip.
- The heel is placed on the floor, with the foot flexed at approximately 90 degrees.



- With arms outstretched, hands overlapping, and middle fingers even, the participant slowly bends forward at the hip joint, reaching as far as possible toward or past the toes.
- If the extended knee starts to bend, ask the participant to move slowly back until the knee is straight.
- The maximum reach must be hold for 2 seconds.
- The participant should practice the test on both legs to see which is preferred (the one resulting in the better score). Only the preferred leg is used for scoring purposes (for comparison with norms).
- Once the preferred leg is determined, have the participant practice two times, administer two test trials and mark the better test score.
- Measure the distance from the tips of the middle fingers to the toe end of the shoe to the nearest half inch (centimeter). The midpoint at the toe end of the shoe represents the zero point. If the reach is short of this point, record the distance as a minus(-) score; if the middle fingers touch the toes, record a score of zero; and if the reach is past the midpoint of the toes, record the distance as a plus(+) score.

• Important Notes
- Place the chair securely against a wall so it doesn't slip during testing.
- Remind participants to exhale as they bend slowly forward and to avoid bouncing.
- Participants should stretch only to a point of slight discomfort, never to the point of pain.
- Remind participants not to hold their breath-just continue breathing throughout the test.
- Do not administer the test to people with severe osteoporosis, with recent knee or hip replacements, or who have pain when flexing forward.

- Tester should get down beside the participant to the outside of the extended leg and place one hand on the knee (gently) so that if the tester feels the knee start to bend, she can have the participant stop or pull back if necessary.

4) Back Scratch Test

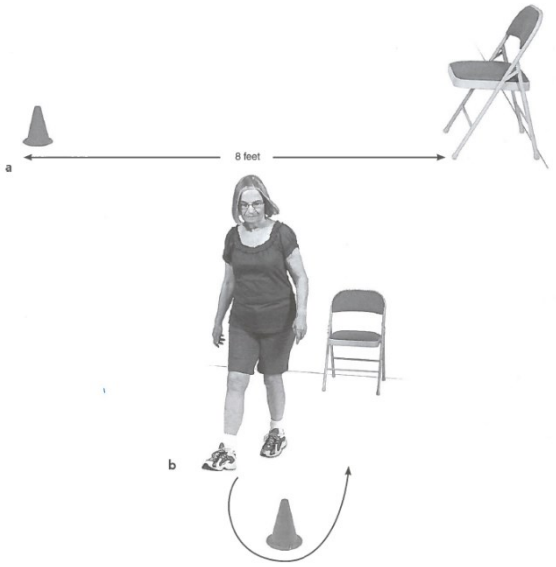
- Purpose
  - To assess upper-body (shoulder) flexibility
- Equipment
  - 18-inch (46 cm) ruler
- Procedure
  - Have the participant stand and place the preferred hand over the same shoulder, palm down and fingers extended, reaching down the middle of the back as far as possible.
  - Note that the elbow is pointed up. Ask the participant to place the other arm around the back of the waist with the palm up, reaching up the middle of the back as far as possible in an attempt to touch or overlap the extended middle
  - fingers of both hands.
  - The participant should practice the test to determine the preferred position (the hand over the shoulder that produces the best score).
  - Two practice trials are given before scoring the test.
  - Check to see if the middle fingers are directed toward each other as best as possible.
  - Without moving the participant's hands, direct the middle fingers to the best alignment.
  - Do not allow participants to grab their fingers together and pull.

  - After giving the participant two warm-up practice trials in the preferred position, administer two test trials and record the better test score to the nearest half inch (cm), measuring the distance of overlap, or distance between, the tips of the middle fingers.
  - Give a minus(-) score if the middle fingers do not touch, a zero score if the middle fingers just barely touch, and a plus (+) score if the middle fingers overlap.
  - Always measure the distance from the tip of one middle finger to the tip of the other, regardless of their alignment behind the back.
- Important Notes

- Stop the test if the participant experiences pain. This test is contraindicated for people with neck and shoulder injuries or problems (e.g., frozen shoulder, rotator cuff problems, pinched nerves).
- Remind participants to avoid any bouncing or rapid movements.
- Try to take the measurement as quickly as possible so participants don't have to hold an uncomfortable position.
- Have participants shake and roll their shoulders between trials.

5) 8-Foot Up-and-Go Test

- Purpose
  - To assess agility and dynamic balance
- Equipment
  - Stopwatch; chair with 17-inch (43 cm) seat height; tape measure; and cone (or similar marker)
- Procedure
  - Place the chair against the wall, facing a cone marker exactly 8 feet (2.4 m) away (a), measured from the back of the cone to a point on the floor even with the front edge of the chair.
  - Instruct the participant to sit in the middle of the chair with back straight, feet flat on the floor, and hands on the thighs.
  - On the signal "go," the participant gets up from the chair, walks as quickly as possible around either side of the cone (b), and sits back down in the chair.



  - Be sure to start the timer on the signal "go" whether or not the participant has started to move, and stop the timer at the exact instant the person sits back down on the chair.
  - After you have demonstrated the proper form and desired pace, have the participant practice the test once, and then administer two test trials. Record the best (fastest) time to the nearest tenth of a second.
  -
- Important Notes
  - When administering the 8-foot up-and-go test, stand between the chair and cone in order to assist participants in case they lose their balance.
  - For the frail, you may need to spot them more closely, especially as they stand, turn around the cone, and sit down.

- If at any time you believe a person is at risk for falling, do not administer the test.
- With a frail or very obese person, watch that he stands up and sits down safely; you may have to direct the person's bottom to the chair as he sits down.

6) 6-Minute Walk Test

- Purpose
  - To assess aerobic endurance
- Equipment
  - Long measuring tape; two stopwatches; cones (or similar markers); chairs for waiting partners and for walkers who need to rest
- Procedure
  - For improved pacing and maximum scoring accuracy, have participants practice a 6-minute walk before test day.
  - The distance between the cones (longest distance including the cone size) is 15 meters.
  - On the signal "go," the participant begins walking as fast as possible (not running) around the course, covering as much distance as possible in the 6-minute time limit.
  - We recommend using two stopwatches to time the test, just in case one stops working.
  - Keep track of the laps and the remaining time should be called out every minute to assist with pacing.
  - Participants can stop and rest on the chairs provided, but the time keeps running.
  - The tester should encourage participants a few times by saying, e.g., "You're doing well," and "Keep up the good work."
  - Count down when the time is at almost 6-minute mark to prevent a sudden stop.
  - At 6 minutes, the tester asks participant to stop and stay right on the stop where stopped.
  - Measure the distance between participant and one of the cones and calculate the total distance.
- Important Notes
  - When administering tests, the 6-minute walk test should always be given last.
  - Select a well-lit walking area with a level, nonslip surface.
  - Position a chair outside of the walking area for participants who want to rest during or after the test and for emergency situations (e.g., dizziness or overexertion).
  - Monitor participants for signs of overexertion.

- Remind participants that they can slow down; or they can stop, rest, and start again until the 6 minutes are up.