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EFFECTIVENESS, FEASIBILITY AND SAFETY OF PHYSICAL EXERCISE FOR BONE HEALTH IN MEN RECEIVING ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER: STATE OF THE ART AND PROPOSAL OF EVIDENCE-BASED INTERVENTION

Candidate Dr. Barbara Bressi

Supervisor Dr. Stefania Costi

Director of the PhD Program: Prof. Giuseppe Biagini

To my family

To my father, mother, and sister

To Carlo for his patience and constant love, encouragement and support

and to my darling, lovely Atena

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List of abbreviations

aBMD = areal bone mineral density

ACSM = American college of sports medicine

ADT = androgen deprivation therapy

AE = aerobic exercise

AerRes = aerobic+resistance exercise

AEs = adverse events

AJCC = American joint committee on cancer

BMD = bone mineral density

BMI = body mass index

BTMs = bone turnover markers

BW = body weight

CCI = Charlson comorbidity index

CDC = centers for disease control and prevention

CG = control group

CI = confidence interval

CONSORT = consolidated standards of reporting trials

CTCAE = common terminology criteria for adverse events

DEXA = dual-energy x-ray absorptiometry

DRE = digital rectal examination

EBRT = external beam radiation therapy

FITT = frequency, intensity, time, type

FSS = fatigue severity scale

FT = football training

GLOBOCAN = global cancer observatory

GnRH = gonadotropin-releasing hormone

GS = Gleason score

HADS = hospital anxiety and depression scale

HE = home-based exercise

HR = heart rate

HRmax = maximum heart rate

IG = intervention group

IE = impact-loading exercise

ImpRes = impact+resistance exercise

L = left

LB = lower body

METs = metabolic equivalents

MMSE = mini mental state examination

6MWT = six minute walk test

NCCN = national comprehensive cancer network

NR = not reported

PACC = physical activity and cancer control

PASSI = progressi delle aziende sanitarie per la salute in Italia

PCa = prostate cancer

PE = physical exercise

PEDro = physiotherapy evidence database

POMA = performance oriented mobility assessment

POMA-B = performance oriented mobility assessment - balance

POMA-G = performance oriented mobility assessment - gait

PRISMA = preferred reporting items for systematic review and meta-analysis

PROSPERO = International Prospective Register of Systematic Reviews

PSA = prostate specific antigen

R = right

RCTs = randomized controlled trials

RE = resistance exercise

1RM = one-repetition maximum

RPE = rate of perceived exertion

RT = radiotherapy

SD = standard deviation

SE = supervised exercise

SF-12 = short form twelve

SPIRIT = standard protocol items: recommendations for interventional trials

STIT = servizio tecnologie informatiche e telematiche

STROBE = strengthening the reporting of observational studies in epidemiology.

TNM = tumor, nodes, metastasis

TRUS= transrectal ultrasound

TTM = transtheoretical model

UB = upper body

UE = unsupervised exercise

WHO = world health organization

WBE = weight-bearing exercise

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ABSTRACT (English version)

Background

Androgen Deprivation Therapy (ADT) has side effects which increase the risk of accidental falls and fractures in men with prostate cancer (PCa). Although physical exercise (PE) and healthy lifestyle are recommended in cancer survivors to counteract the side effects of treatment, few individuals comply with the recommended level of PE.

Objectives

The aim of this Ph.D. research thesis is to ascertain the effectiveness of PE on bone health (bone mineral density (BMD), accidental falls and fractures), and to verify its feasibility and safety in patients with PCa receiving ADT.

Methods

Two systematic reviews were conducted. We searched in MEDLINE, EMBASE, CINAHL and the Cochrane Library for randomized controlled trials (RCTs) investigating the effectiveness of PE on bone health and, also its feasibility and safety in men with PCa receiving ADT. A cross-sectional study was conducted in an Italian hospital setting to describe the lifestyle of individuals with PCa. Men newly diagnosed with PCa were consecutively invited to participate in a structured interview that was conducted either in person or by telephone. We collected data on their PE habits and motivation to change towards healthier behaviors. Furthermore, we designed an ongoing pilot study that examines the feasibility and safety of a multicomponent experimental PE intervention in patients with PCa that are currently receiving ADT associated with radiotherapy. This PE intervention is aligned with individual preferences, it addresses psychophysical and cognitive functions, and it is specifically targeted at preventing accidental falls and fractures with an appropriate volume of exercise.

Results

None of the RCTs included in the two systematic reviews investigated the risk of accidental falls and fractures. Nevertheless, preliminary data suggest that multicomponent PE interventions are likely to be effective in reducing BMD loss, especially when involving resistance and impact-loading exercise or football training. Although PE seems feasible in patients with PCa receiving ADT, football training should be prescribed with caution for safety reasons. More than half of the men interviewed in the cross-sectional study (21 out of 40) did not reach the recommended PE level for cancer survivors, and were not willing to change their lifestyle. However, 40% of the sample reported their interest in participating in an exercise program. To date, five participants have been included in the ongoing pilot study: in addition to data on feasibility and safety of the experimental intervention, we investigate its impact on muscle strength, balance, fatigue, mood disturbances, cognitive function, quality of life, and participants’ satisfaction with the intervention. We are also going to record the number of accidental falls and fractures occurring during the intervention, up to one year of follow-up.

Conclusions

PE is recommended to counteract the side effects of ADT in individuals with PCa. Nevertheless, the evidence of the effectiveness of PE to prevent the risk of accidental falls and fractures and the loss of BMD is lacking. Multicomponent PE targeting bone health seems feasible and safe in this population, but adverse events should be systematically documented, according to current guidelines. Our data suggest that a relevant proportion of the men newly diagnosed with PCa are insufficiently active and, even when exposed to behavioral risk factors, they are not willing to change their lifestyle. Health-care professionals who deal with this population should take advantage of the teachable moment and apply strategies that support patients' motivation to exercise and adherence to healthier lifestyles.

Keywords

prostatic neoplasms; androgen deprivation; exercise; accidental falls; healthy lifestyle

ABSTRACT (Italian version)

Introduzione

La terapia di deprivazione androgenica (TDA) causa svariati effetti collaterali che aumentano il rischio di cadute accidentali e fratture negli uomini con cancro alla prostata (PCa). Anche se l'esercizio fisico (EF) e uno stile di vita sano sono raccomandati nei sopravvissuti al cancro per contrastare gli effetti collaterali del trattamento, pochi individui rispettano il livello di EF raccomandato.

Obiettivi

L'obiettivo di questa tesi di dottorato è accertare l'efficacia di un programma di EF nel prevenire la salute delle ossa (densità minerale ossea (DMO), cadute accidentali e fratture), e di verificarne la sua fattibilità e sicurezza nei pazienti con PCa che ricevono TDA.

Metodi

Sono state condotte due revisioni sistematiche della letteratura. Abbiamo cercato in MEDLINE, EMBASE, CINAHL e Cochrane Library studi randomizzati controllati che valutassero l'efficacia dell'EF sulla salute delle ossa, e anche la sua fattibilità e sicurezza negli uomini con PCa che ricevono TDA. Abbiamo condotto uno studio osservazionale nel territorio di Reggio Emilia per descrivere lo stile di vita e le abitudini di EF dei pazienti con nuova diagnosi di PCa, invitandoli a partecipare ad una intervista svolta di persona o per telefono. Inoltre, abbiamo progettato uno studio pilota in corso che esamina la fattibilità e sicurezza di un intervento sperimentale di EF multicomponente in pazienti con PCa che attualmente ricevono TDA associata a radioterapia. Questo intervento allineato con le preferenze individuali, rivolto alle funzioni psicofisiche e cognitive, è specificamente mirato a prevenire cadute accidentali e fratture con un adeguato volume di esercizio.

Risultati

Nessuno degli studi inclusi nelle due revisioni sistematiche ha indagato l'efficacia di un programma di EF nel prevenire cadute accidentali e fratture. Tuttavia, i dati preliminari suggeriscono che interventi di EF multicomponenti sono probabilmente efficaci nel ridurre la perdita di DMO, soprattutto quando comprendono esercizi di rinforzo muscolare e di impatto o l'allenamento di calcio. Anche se l'EF sembra fattibile nei pazienti con PCa che ricevono TDA, l'allenamento di calcio dovrebbe essere prescritto con cautela per motivi di sicurezza. Più della metà degli uomini intervistati nello studio osservazionale (21 su 40) non raggiungeva il livello di EF raccomandato per i sopravvissuti al cancro, e non erano disposti a cambiare il loro stile di vita. Tuttavia, il 40% del campione ha riferito il proprio interesse a partecipare ad un programma di EF. Ad oggi, cinque partecipanti sono stati inclusi nello studio pilota in corso: oltre ai dati sulla fattibilità e sicurezza dell'intervento sperimentale, indaghiamo il suo impatto su forza muscolare, equilibrio, fatigue,

disturbi dell'umore, funzione cognitiva, qualità della vita e soddisfazione dei partecipanti. Registreremo anche cadute accidentali e fratture che si verificano durante l'intervento, fino a un anno di follow-up.

Conclusioni

L'EF è raccomandato per contrastare gli effetti collaterali della TDA negli uomini con PCa. Tuttavia, ad oggi mancano prove dell'efficacia dell'EF nel prevenire cadute accidentali e fratture e la perdita di DMO. I programmi di EF multicomponente sembrano fattibili e sicuri in questa popolazione, ma gli eventi avversi dovrebbero essere sistematicamente documentati secondo le attuali linee guida. I nostri dati suggeriscono che una parte rilevante degli uomini con nuova diagnosi di PCa non è sufficientemente attiva, e anche quando esposti a fattori di rischio comportamentali, non sono disposti a cambiare il loro stile di vita. Gli operatori sanitari dovrebbero approfittare del momento della diagnosi e applicare strategie per motivare i pazienti alla pratica di EF e all'adesione a stili di vita più sani.

Parole chiave

cancro alla prostata; terapia ormonale; esercizio fisico; cadute; stile di vita.

GENERAL INTRODUCTION AND Ph.D. SCIENTIFIC ACTIVITIES REPORT (2018-2021)

As in other industrialized regions, prostate cancer (PCa) is the most commonly diagnosed cancer in men in Europe, with incidence increasing with age. Due to both screening and current treatments for PCa, the survival rate is over 90% worldwide. Nevertheless, these patients are vulnerable because of treatment side effects and because of their age.

Androgen deprivation therapy (ADT) is a common hormone treatment used in PCa patients with advanced and metastatic disease to prolong survival.

However, ADT causes severe hypogonadism, which induces several side effects, particularly musculoskeletal, cardiometabolic, and cognitive health issues.

It has been reported that during the first 3-12 months of ADT, men have a dramatic decrease in bone mineral density (BMD) and muscle mass and a deterioration in cognitive function, which may explain the higher fractures and accidental fall rates observed in this population.

Thus, there is a need to develop safe, effective interventions to manage the multiple treatment-induced side effects of ADT in men with PCa.

Physical exercise (PE) is strongly suggested as an intervention to mitigate a variety of side effects of PCa treatments. In terms of musculoskeletal and cardiometabolic outcomes, PE can increase muscle mass and strength, decrease fat mass, and control body weight in men treated with ADT. Furthermore, the guidelines for cancer survivors recommend PE because of its favorable effects on physical function, performance, quality of life, anxiety, and depression. What's more, PE can improve several health outcomes in healthy older adults, such as BMD, accidental falls and fracture risks, and cognitive function. However, as these improvements have not yet been ascertained, they could be confirmed in the vulnerable population of men with PCa.

A pivotal aspect to consider in PE interventions is the type and optimal dosage required to improve clinically relevant outcomes as well as their safety and feasibility. In fact, a key consideration is whether or not cancer survivors can tolerate the doses of PE hypothesized to effectively improve health outcomes. Thus, reporting both FITT characteristics (frequency, intensity, time, and type) and the adherence to the prescribed exercise is required to identify which PE prescriptions effectively obtain the expected health benefits in cancer survivors.

Therefore, this PhD project was developed through a succession of phases of increasingly in-depth, advanced knowledge during the 3-year course as follows:

First year

The main activities I carried out in the first year were developing the research project, selecting and appraising the literature in this field, and conducting the initial data synthesis. At the same time, I submitted the protocol of the observational study to the Local Ethics Committee; after having obtained its approval, I started recruiting the participants and conducted the first interviews of this study.

I also collaborated on the submission of the research project to a call for the Manodori Grant Foundation and obtained the financial support necessary to develop the experimental part of the project.

As for additional scientific activities, I collaborated on another research project regarding the rehabilitation of children with cerebral palsy, which was conducted at the Unit of Children Rehabilitation for Severe Developmental Disabilities (UDGEE). I contributed with the recruitment of the patients and the implementation and delivery of the experimental rehabilitation interventions. I also collaborated in the writing of three manuscripts in this field, published between 2019 and 2020 (see next chapter for details of the publications).

Second year

Much of my work during the second year focused on the data collection, analysis, and writing of two systematic reviews, one published in 2020, and the second accepted for publication in 2021. Preliminary data on the feasibility and safety of exercise on bone health in patients with PCa receiving ADT were presented as poster at the Annual Meeting 2020, with the theme “Health 4.0: Designing Tomorrow`s Healthcare”, organized by Coimbra Health School, which should have taken place on 19-21 March 2020 in Coimbra (PT) but, due to the COVID-19 pandemic, was postponed to 25-27 June 2020 and held online (Appendix I).

Meanwhile, I continued recruiting and interviewing participants in the observational study. I also drafted the protocol of a pilot experimental feasibility study, its brochure (Appendix II), and its flyer (Appendix III) to facilitate patient engagement and adherence. I submitted this study protocol to the Local Ethics Committee for approval and the article manuscript to an international scientific journal for publication.

I continued to collaborate on the research project regarding the rehabilitation of children with cerebral palsy. Furthermore, during the first year of the COVID-19 pandemic, I collaborated on the development and implementation of an epidemiological study investigating the lifestyle habits of the citizens of Reggio Emilia during the first lockdown (March-May 2020). I collaborated in data analysis and writing of two manuscripts. In the same period, I contributed to drafting a Letter to the Editor regarding respiratory rehabilitation in patients with COVID-19, which was published.

Third year

Most of my work focused on completing the data collection and analyzing the data of the observational study. I wrote the manuscript, which is currently under submission to an international scientific journal.

Preliminary data on the exercise and lifestyle habits of patients with PCa were presented as a poster entitled "Physical exercise and lifestyle behaviours among men with prostate cancer: a cross-sectional study" at the World Physiotherapy Congress 2021, held online 9-11 April 2021 (Appendix IV).

I also started the recruitment and the activities related to the experimental feasibility study. Specifically, I conducted the assessments and completed the five-month intervention of the first three patients included, while two patients are currently attending the exercise program. I submitted the protocol of this experimental feasibility study to an international scientific journal; it is currently under peer review.

I collaborated in the writing of an experimental study protocol on pediatric rehabilitation, which was accepted for publication by an international scientific journal in 2021.

DISSEMINATION ACTIVITIES: PUBLICATIONS AND PRESENTATIONS FROM THE THESIS

Publications related to this project

Bressi B, Cagliari M, Contesini M, Mazzini E, Bergamaschi FAM, Moscato A, Bassi MC, Costi S. Physical Exercise for Bone Health in Men with Prostate Cancer Receiving Androgen Deprivation Therapy: a Systematic Review. *Support Care Cancer* **2021** Apr; *29*, 1811-1824 doi:10.1007/s00520-020-05830-1.

Cagliari M, Bressi B, Bassi MC, Fugazzaro S, Prati G, Iotti C, Costi S. Feasibility and Safety of Physical Exercise to Preserve Bone Health in Men with Prostate Cancer Undergoing Androgen Deprivation Therapy: a Systematic Review. Accepted for publication by *Phys Ther,* Nov 21, **2021**.

Submitted article related to this project

Bressi B, Iotti C, Cagliari M, Cavuto S, Fugazzaro S, Costi S. Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study protocol. Submitted and under revision to: *BMJ open,* January 11, **2021**.

Bressi B, Iotti C, Cagliari M, Fugazzaro S, Cavuto S, Bergamaschi FAM, Moscato A, Costi S. Physical Exercise Habits, Lifestyle Behaviors, and Motivation to Change Among Men with Prostate Cancer: A Cross-Sectional Study. Submitted to: *Support Care Cancer*, Nov 19, **2021**.

Oral presentations related to this project

VIII Congresso Nazionale Società Italiana di Fisioterapia (SIF) “La posologia dell’Esercizio in Fisioterapia tra evidence e expertise” Oct. 26–27, 2019 Venezia Mestre Ospedale Dell’Angelo.

Leanings Day – Liceo Virgilio Mantova, “Attività fisica e prevenzione del cancro: attualità e nuove prospettive”, Febr. 15, 2020.

First Journal Club of Physical Medicine and Rehabilitation Unit – Azienda USL-IRCCS di Reggio Emilia. “Esercizio fisico e neoplasia prostatica”, June 22, 2020.

Webinar training event for students of the Course of Bachelor’s Degree in Physiotherapy of the University of Genova, Torino, Modena and Reggio Emilia, Udine, Trieste. Speech title “Il carcinoma prostatico: esercizio fisico nel paziente oncologico” Jul 27, 2020.

“Notte dei ricercatori” event – University of Modena and Reggio Emilia. Speech title “Il ruolo dell'esercizio fisico nella prevenzione e nella cura delle Malattie Oncologiche” Nov 27, 2020.

Guest at the Telereggio TV program “Buongiorno Reggio”. Speech title “Esercizio fisico e prevenzione” Dec 10, 2020.

Leanings Day Webinar for "A. Moro" and "Istituto d’Arzo" High school of Reggio Emilia and Montecchio Emilia with a speech entitled “Attività fisica e prevenzione del cancro: attualità e nuove prospettive”, Jan 28, 2021.

Educational event for the coaches of the UISP (Unione Italiana Sport Per tutti) of Reggio Emilia with a speech entitled " Esercizio fisico e prevenzione". Jan 30, 2021.

Leanings Day Webinar for “E. Gadda” High School of Fornovo (PR) with a speech entitled “Attività fisica e prevenzione del cancro: attualità e nuove prospettive” Feb 18, 2021.

Other publications during the 3-year course

Errante A, Bozzetti F, Sghedoni S, Bressi B, Costi S, Crisi G, Ferrari A, Fogassi L. Explicit motor imagery for grasping actions in Children with spastic Unilateral Cerebral Palsy. *Front Neurol* **2019** Aug; *10,* 837. Doi: 10.3389/fneur.2019.00837.

Costi S, Mecugni D, Beccani L, Alboresi S, Bressi B, Paltrinieri S, Ferrari A, Pelosin E. Construct Validity of the Activities Scale for Kids Performance in Children With Cerebral Palsy: Brief Report. *Dev Neurorehabil* **2020** Oct; *23*, 474-477. Doi: 10.1080/17518423.2020.1764649.

Costi S, Bressi B, Cavuto S, Braglia L, Ferrari A, Pelosin E. Cross-cultural Validation of Activities Scale for Kids: The Performance of Healthy Italian Children. *J Sports Med Phys Fitness* **2020** Jul; *60*: 1014-1019. Doi: 10.23736/S0022-4707.20.10466-3.

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Verzelloni J, Errante A, Beccani L, Filippi MC, Bressi B, Cavuto S, Ziccarelli S, Costi S, Pineschi E, Fogassi L, Ferrari A. Can a pathological model improve the abilities of the paretic hand in hemiplegic children? The PAM-AOT study protocol of a randomized controlled trial. Accepted for publication by: *BMJ Open*, Dec 1, **2021**.

CHAPTER I

Introduction

Worldwide, about 30 million new cases and 16 million new deaths from all cancers are expected by the year of 2040 [1]. In this context, PCa is the third most prevalent cancer, and with 4,956,901 cases accounting for 16.2% of all prevalent cancers globally in 2020 [2]. Further, as risk increases significantly with age, PCa is the most commonly diagnosed malignancy worldwide among men over the age of 50 both in terms of prevalence and incidence [2].

The increase in life expectancy, the increased early diagnosis with prostatic specific antigen (PSA) screening, and better treatments have led to a decline in the mortality rate for PCa over the past several years in many developed countries [3,4]. Unfortunately, many survivors of PCa experience physical and psychosocial late and/or long-term effects of treatment, which can lead to a higher risk of morbidity and disability, with a poorer quality of life [5]. For that reason, clinical interventions aimed at promoting physiological and psychological well-being and at improving quality of life are relevant to people with PCa, both in terms of disability and of economic burden [6,7].

Given the known beneficial effects of PE on the healthy population [8], PE has been suggested as a strategy to reduce the side effects of cancer treatments for PCa [9,10], with potential positive effects on health care costs and patients' quality of life [10–12]. Therefore, this thesis aimed to implement evidence-based cancer rehabilitation in patients with PCa.

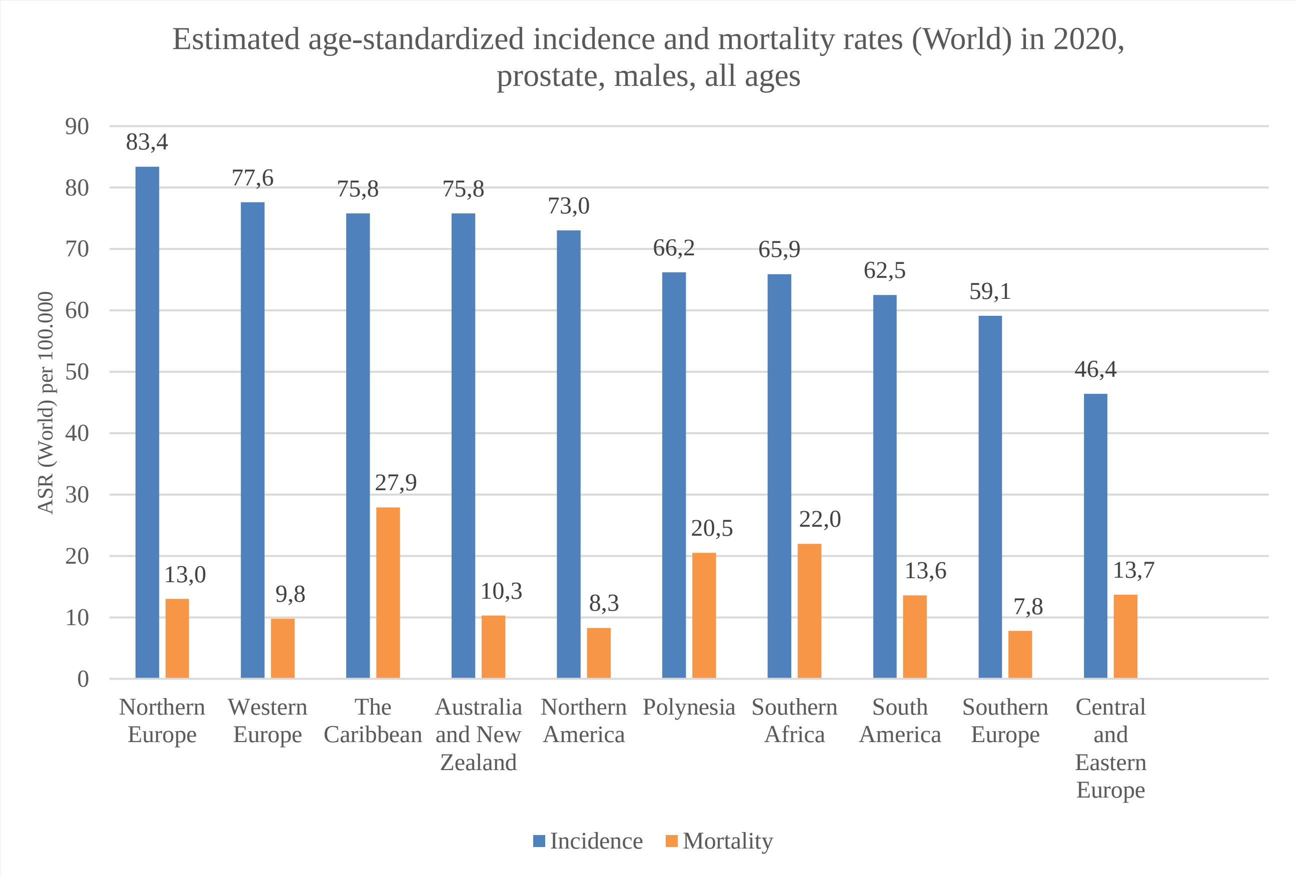
Epidemiology of PCa

Incidence. PCa is the fourth most frequently diagnosed cancer worldwide [3,13], with around 1,414,259 new cases in 2020 (accounting for 11.6% of all cancer diagnoses) [2]. Higher incidence is registered in Northern and Western Europe, the Caribbean, Australia/New Zealand and Northern America (Figure 1.1) [2]. In Italy, PCa accounts for about 19% of all tumors diagnosed among males, with an estimated 36,000 new cases in 2020 [14].

Mortality. PCa is the fifth leading cause of cancer death in men globally, with high mortality rates in Sub-Saharan Africa and the Caribbean [3]. An estimated 359,000 males worldwide died from PCa in 2018 (3.8% of all cancer deaths) [3]. Despite decreasing estimates of mortality rates from 2015 to date (-14.6%), in 2021 PCa remains the estimated fourth leading cause of cancer death among males in Italy [14].

Survival. In developed countries, PCa survival rates have steadily improved over the past decades. The most recently reported 5-year survival rate is 98% in 2021 in the United States [15]. In Italy, the five-year survival rate after diagnosis is currently 91% [14], but this percentage continues to rise as a result of widespread PSA testing since the 1980s, resulting in earlier detection of indolent PCa cases [15].

Figure 1.1 Estimated age-standardized incidence and mortality rates in 2020, prostate, males, all ages world areas. Adapted from global cancer observatory (GLOBOCAN) 2020 [2].



Etiology and diagnosis of PCa

PCa represents a spectrum of diseases that range from a nonaggressive, slow-growing disease that does not require any treatment to an aggressive, fast-growing disease that does. The risk factors for PCa include age, family history, race, and some genetic variations as well as environmental and lifestyle factors [16–18].

Diagnosis is based on several approaches, used alone or in association: (1) digital rectal exam (DRE), (2) PSA dosage, (3) imaging, (4) prostate biopsy. According to the Prostate Cancer Referral Working Group guidelines, the indication to biopsy is based on clinical suspicion deriving from DRE and/or PSA, with any available additional clinical information and assessment of any risk factors [19].

The aim of the early detection strategies is to diagnose aggressive PCa that is potentially curable, while minimizing unnecessary procedures, as well as indolent disease [16]. The introduction of PSA screening has contributed to the detection of PCa at an earlier stage, with the aim of decreasing mortality rates [4,16]. Although this likely contributes to a reduction in mortality, a significant number of indolent cases that might never progress to becoming clinically overt are also detected (overdetection), many of which are treated, leading to the phenomenon of overtreatment [16,20]. Therefore, to date, the US Preventive Services Task Force guidelines recommend against the adoption of population-based screening policies [20].

Staging and grading of PCa

The widely accepted system used to indicate disease stage in PCa is the T (tumor extent) N (lymph node invasion) M (presence or absence of metastasis) system by the American Joint Committee on Cancer (AJCC) [21]. There are two types of staging: clinical staging is determined by DRE and radiologic results, Gleason score (GS) and grade group, the extent of cancer in the biopsy specimens, and serum PSA level [22]; pathologic staging is assigned based on the histological examination performed by the pathologist [23].

Grading is the degree of differentiation of the tumor cells and indicates its aggressiveness. In PCa, grading is calculated using the GS and the grade group, recently updated based on a new classification, which identifies five glandular architectural features that are assigned an increasing malignancy score [24].

TNM staging, used in combination with tumor grade and PSA dosage, is regarded as a well-accepted practice standard for PCa and is used as the basis for guiding treatment decision making.

Furthermore, optimal treatment of PCa requires assessment of the risk of how likely a given cancer to spread to the regional lymph nodes or progress with metastasis after treatment [22]. The National Comprehensive Cancer Network (NCCN) guidelines have incorporated a risk stratification scheme that uses stage, GS and grade group, and PSA to assign patients to a risk group. These risk groups are used to select the appropriate options that should be considered and to predict the probability of biochemical recurrence after definitive local therapy [22]. The NCCN guidelines categorize five local risk groups in PCa: very low, low, intermediate (favorable, unfavorable), high, and very high [22].

PCa treatments

The treatment options for men with PCa can be local, systemic, or a combination of both. The treatment choice depends on several factors such as stage and grade of cancer at diagnosis, risk of progression, life expectancy, age, and comorbidities as well as on the patient's own preferences and the side effects of treatment [22].

Local treatment includes surgery (prostatectomy) and radiotherapy (RT), while systemic treatment includes hormone therapy and chemotherapy. As an alternative to these active treatments, "watchful waiting" and "active surveillance" strategies could also be used [5]. Although treatment can slow down the progression of PCa and can increase the survival rate, there are numerous side effects that worsen quality of life [5]. Table 1.1 summarizes the main characteristics of each treatment and their side effects.

Table 1.1 Description of the characteristics of PCa option treatments and related side effects [5,25].

PCa option treatments	Local/Systemic	Description	Side effects
Active surveillance	-	Patients receive no cancer treatment but will have tests, including biopsies, on a regular basis to monitor eventual changes in tumor growth.	Stress, anxiety, worry, risks associated with repeat biopsy, PSAs and DREs, symptoms associated with disease progression.
Watchful waiting	-	Patients receive no cancer treatment, but condition is monitored until signs or symptoms appear or change. Treatment is given to relieve symptoms and improve quality of life.	Stress, anxiety, worry, risks associated with repeat PSAs and DREs, symptoms associated with disease progression.
Surgery	Local	Surgery is a procedure to remove cancer from the body. The tumor is removed along with some normal-looking prostate tissue around its edge called the surgical margin.	Postoperative urinary incontinence and dysfunction, sexual dysfunction.
Radiotherapy	Local	RT uses high-energy radiation from x-rays, gamma rays, and other sources to kill cancer cells and shrink tumors. There are two main types of radiotherapy: - EBRT uses a machine outside of the body; - Brachytherapy is internal radiation delivered inside the body.	Urinary incontinence and dysfunction, sexual dysfunction gastrointestinal symptoms, fatigue, second cancer (bladder, colorectal, rectum).
Hormone therapy	Systemic	Hormone therapy is a treatment that removes hormones or blocks their action and stops cancer cells from growing. In PCa, male sex hormones can cause cancer to grow. ADT consists of drugs, surgery, or other hormones used to reduce the amount of male	Hot flashes, urinary dysfunction, sexual dysfunction, loss of libido, musculoskeletal alterations, cognitive and mood disturbances, fatigue, cardiovascular disease.

		hormones or block them from working.	
Chemotherapy	Systemic	Chemotherapy is a treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body.	Fatigue, mouth sores, nausea, hair loss.

Abbreviations: PCa, prostate cancer; PSAs, prostatic specific antigens; DREs, digital rectal exams; RT, radiotherapy, EBRT, external beam radiation therapy; ADT, androgen deprivation therapy.

Side effects of androgen deprivation therapy

Over the past two decades, the number of men with PCa who receive androgen deprivation therapy (ADT) as treatment has increased dramatically [26]. ADT is the first-line treatment for intermediate or high risk disease and for advanced and metastatic cancer. In addition, it is used as neoadjuvant, adjuvant, and concurrent therapy with prostatectomy and radiotherapy (RT). It is also continued when the cancer becomes castration-resistant [22,27].

ADT is managed either surgically, with bilateral orchiectomy, or pharmaceutically, using gonadotropin-releasing hormone (GnRH) agonists or antagonists; both approaches lead to hypogonadism [28,29]. The overall aim of ADT in PCa is to reduce testosterone levels, thereby minimizing an important stimulus to androgen-sensitive PCa cells and causing their apoptosis [28,29].

The treatments for PCa that focus on reducing the levels or effects of androgen by ADT have many undesirable side effects. Hypogonadism has a negative impact on the metabolism and on muscle and bone tissues through decreases in testosterone levels, resulting in a large variety of side effects. Some of these include musculoskeletal and metabolic changes (increased fat mass, reduction of muscle and bone mass and strength) cardiovascular and reproductive system disorders, fatigue, and cognitive impairment, which have negative implications for physiological and psychological function [30,31]. All the musculoskeletal alterations contribute to developing sarcopenia, osteopenia, and osteoporosis, with a consequent increased risk for low trauma or fragility fractures [30–34]. In fact, a study by Shahinian et al. [35] showed that PCa survivors who received ADT had a higher risk of fracture than those who had never received ADT (19.4 vs. 12.6%, respectively), reconfirmed by several subsequent studies [32,33,36,37]. A recent meta-analysis suggests that there is a 1.59% significant loss in hip areal bone mineral density (aBMD) (95% CI -2.99 to -0.19, p=0.03) and 3.6% in lumbar spine aBMD (95%

CI -6.72 to -0.47, *p*=0.02) [38]. This BMD loss is associated with the decay of both cortical and trabecular bone structure [39]. Accelerated aBMD loss has also been observed at the femoral neck, radius, and whole body, indicating that ADT has a systemic effect on bone [38–40]. The rate of bone loss tends to be higher early in treatment, but remains elevated also after starting ADT [34,40], at the rate of approximately 0.5% per year bone loss in healthy middle-age and older adults [41]. Furthermore, sarcopenia is associated with a higher rate of accidental falls and a higher incidence of hospitalizations [42]. In fact, men who have been exposed or are exposed to ADT are more than twice as likely to fall as those not exposed (37% and 34% vs 15%) [43]. Hence, in PCa patients treated with ADT, accidental falls and fractures significantly impact health-related quality of life and increase the risk of hospitalization and death [32,44]. This is further worsened by a frailty condition commonly associated with the advanced age at which cancer is diagnosed and the use of ADT, which causes muscle loss and strength [43]. In healthy older adults, age-related loss in lean tissue mass is about 1.0% per year [45]. However, a pooled data meta-analysis of 573 men receiving ADT showed a body lean mass loss of 2.8% (95% CI -3.6 to -2.0, $p<0.0001$) and fat mass increase of 7.7% (95% CI 4.3 to 11.2, $p<0.0001$), body weight increase of 2.1% (95% CI 1.35 to 2.94, $p<0.0001$), and increase in BMI of 2.2%, (95% CI 1.16 to 3.14, $p<0.0001$) [46].

Moreover, although the effects of ADT on cognition are still uncertain, initial evidence seems to identify a correlation between ADT and cognitive deficit, dementia, and mood disorders [47–49]. Further studies should investigate this association as it could act as an additional risk factor for accidental falls and fractures [50]. Fatigue is another aspect to consider that could contribute to a higher risk of accidental falls [51]. Current evidence confirms the presence of fatigue in men treated with ADT and ADT in association with RT, and this symptom worsens quality of life [52].

The potential mechanisms of PE to prevent accidental falls and fractures

Low BMD greatly increases the risk of fractures with minimal trauma, as with accidental falls [53]. Thus, strategies that maximize bone mass and/or reduce the risk of falls have the potential to reduce morbidity and mortality from osteoporotic fractures [33]. Existing treatments to alleviate ADT side effects on bone health are predominantly pharmaceutical [54]. However, these treatments are expensive, and their effects do not translate into improved physical function, muscle mass and strength, or decreased levels of fatigue [55]. Instead, PE can potentially increase bone mass and reduce the risk of accidental falls [56,57]. In fact, PE has been recommended by the guidelines for osteoporosis prevention and treatment in healthy populations, with the best evidence (grade A) [41,56,58,59]. What is known, primarily from animal studies, is that increased mechanical loads placed on bone through both impact and muscle forces cause deformation of the whole bone [41,60]. Bone responds to PE through additions of new bone in both cortical and trabecular regions and results in adaptation through periosteal expansion, reducing porosity and changing bone structure [60,61]. Therefore, in addition to the effect on mass and density, the increased mechanical loading induced by PE may influence structural changes in bone to increase strength in response to the new loading condition [58,62]. To obtain an osteogenic stimulus, bone must be subjected to a strain higher than a threshold determined by the habitual strain range [61,63]. The threshold varies among individuals according to PE habits: inactive individuals respond to low-impact loading and improve bone mass or structure, while more active individuals will need a higher mechanical load to promote a skeletal response [41,64]. Thus, individuals may respond differently to similar mechanical loading conditions. Because it takes 3-4 months for one remodeling cycle to complete the sequence of bone resorption, formation, and mineralization, a minimum of 6-8 months is required to achieve a new steady-state bone mass that is measurable [41].

Weight-bearing endurance exercise (i.e., jogging, walking), activities that involve jumping, and resistance exercise are recommended to prevent bone loss in the adult and elderly populations [41]. Nevertheless, the research available for the dose-response needed to determine the volume of PE required to impact on bone is scarce. Therefore, the characteristics of PE that guarantee an osteogenic stimulus, such as frequency, intensity, type, and time (FITT model), are not yet completely understood [41,58,62].

There is little evidence from a prospective study that PE reduces the incidence of vertebral fractures [65], and that sedentary behavior is a risk factor for hip fractures [66,67]. Nevertheless, there are no randomized controlled trials (RCTs) on the effectiveness of PE to reduce fractures. This lack could be due to the necessity to include a large sample size and the required long period of observation [41]. Regular PE may help to prevent fractures not only by preserving bone mass but also by reducing the incidence of accidental falls [57,68].

In fact, the positive effects of PE are not only limited to the bone structure but also include muscle benefits. Moreover, it is suggested that lean mass is among the strongest correlates of bone mass, density, and structural strength, reducing the bone stress in the healthy adult population [69,70]. The molecular mechanisms that induce the skeletal muscle adaptation to PE consist in a gradual alteration in protein content and enzyme activities with structural remodeling and long-term functional adjustments [71,72]. These muscle adaptations to PE result in a favorable effect on body composition, increasing lean body mass and strength and decreasing fat mass [73]. Evidence suggests that aerobic exercise is the most effective modality to reduce fat mass and body weight, while resistance exercise seems necessary for increasing lean mass in the adult and older population [73–75].

Finally, human and animal studies suggest that PE can stimulate improvement in cerebrovascular function, perfusion, and neuroplasticity in the brain, which may prevent the progressive loss of cognitive function associated with ageing and disorders such as dementia [76,77]. Evidence suggests that aerobic, resistance, and/or multicomponent PE interventions have favorable effects on cognitive function [78].

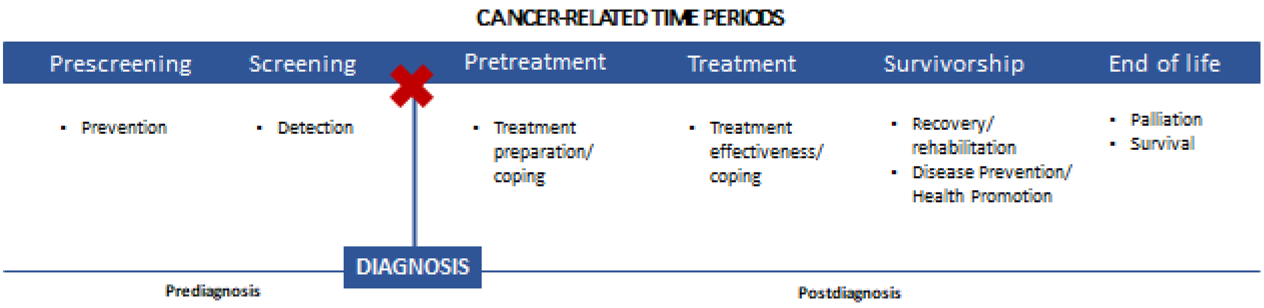
Given all these musculoskeletal and cognitive benefits, PE is likely to have a fall prevention effect through its impact on these key fall risk factors. In fact, PE programs reduce the rate of accidental falls and the number of older people experiencing falls with high-certainty evidence [57]. PE programs that reduce falls primarily involve multicomponent programs including both resistance and balance exercises and programs that include balance and functional exercises [57].

Exercise and cancer research overview

Evidence supporting the benefits of PE in individuals with cancer has grown exponentially over the past two decades. Given the considerable, strong evidence demonstrating the benefits of PE in healthy populations [8], the data produced in this field of research have led the authoritative American Cancer Society (ACS) and American College of Sports Medicine (ACSM) to recommending it in their recent guidelines for cancer prevention and for cancer survivors [79–81].

Already in 2008, Courneya and Friedenreich theorized and updated the framework of physical activity research across the entire cancer continuum (Figure 1.2). The Physical Activity and Cancer Control (PACC) framework summarizes the primary goals of physical activity during each stage of cancer treatment [82]. Courneya and Friedenreich identified two distinct periods before diagnosis and four periods after diagnosis, each with its own specific objectives for physical activity interventions. Therefore, the cumulative evidence supports the promotion of physical activity and the use of PE science principles to gain and maintain physiological, functional, and quality of life benefits during and after cancer treatments [81]. This evidence suggests including exercise during routine care, regardless of any potential benefits on survival outcomes, which are still to be determined [79].

Figure 1.2 Physical activity and cancer control (PACC) framework adapted from Courneya et al., 2007 [82].



In fact, to date, the growing body of new epidemiologic evidence suggests that PE decreases the risk for seven types of cancers (colon, breast, kidney, endometrium, bladder, stomach cancer, and esophageal adenocarcinoma) [79]. Furthermore, emerging data support the hypothesis that PE may extend survival for breast, PCa, and colorectal cancers (21-45% lower mortality risk) [79,83,84]. The findings of a recent meta-analysis on a sample of almost 4 million participants suggest that the amount of physical activity meeting the current World Health Organization (WHO) recommendations provides significant protection against death from cancer [85]. Accordingly, patients should engage in moderate intensity aerobic exercise for at least 150 min/week or in vigorous intensity aerobic exercise for at least 75 min/week, or in an equivalent combination of moderate and vigorous intensity exercise [85–87].

Along with the effects of exercise on survival, PE has an impact on the quality of life and psychosocial well-being of cancer survivors [81].

Some of the beneficial effects of PE on the musculoskeletal, cardiovascular, and metabolic systems have already been demonstrated not only in the general population but also in cancer survivors [81]. The guidelines for people living with cancer [81,86] support following the PE recommendations for the general public. Furthermore, the specific recommendations for frequency, intensity, time, and type (FITT) of PE needed to alleviate the side effects of treatment and improve cancer-related outcomes are currently available [81,86]. To overcome the most common side effects and improve health, these recommendations suggest moderate intensity aerobic exercise for a minimum of 30 minutes, three times per week [81]. In addition, resistance exercise using at least two sets of 8-15 repetitions at least 60% of the individual's one-repetition maximum (1RM) effort should be performed at least twice a week [81,86]. The above-mentioned recommended dose should be performed regularly to achieve any long-lasting effects, to the point that it becomes part of a healthy lifestyle [88].

The ACSM Exercise Guidelines for Cancer Patients and Survivors includes a list of common cancer-related outcomes for which the above-mentioned dose of PE may have a relevant therapeutic benefit

[81]. The level of evidence of the effectiveness of PE on the outcomes investigated was categorized into strong, moderate, or insufficient [81]. The specific dose of resistance exercise, aerobic exercise, and a combination of both is recommended, supported by compelling evidence of the benefits in terms of health-related quality of life, physical functioning, fatigue, and anxiety and depression symptoms [81,89,90]. Some of the acute and persistent effects of cancer treatments can be positively influenced by PE, such as lymphedema in patients with breast cancer, but this effect may not be achieved for lymphedema following other cancer sites (i.e., head and neck, bladder, melanoma, gynecologic) [81].

The evidence on the potential benefits of PE on BMD in cancer survivors is classified as moderate due to the fact that the results are still controversial [81,91], despite the fact that the PE interventions proposed comply with the recommendations of guidelines for exercise and bone health [41]. In fact, in contrast with the study by Dalla Via et al. [91], a recent meta-analysis (2021) in patients principally with breast cancer and PCa suggested that exercise improved hip BMD (effect size = 0.112, 95% CI 0.026 to 0.198; p=0.011) and lumbar spine BMD (effect size = 0.269, 95% CI 0.036 to 0.501; p=0.024) compared to controls [92].

Insufficient evidence exists for the effectiveness of PE on the risk of falls and fractures due to the lack of RCTs with these clinically relevant outcomes [81].

Moreover, cognitive function is currently investigated in exercise trials, but the evidence in humans is limited [93]. Furthermore, in human studies, cognitive function has been measured using self-reported measures, limiting the generalizability of the results [93,94].

Thus, according to the guidelines for cancer survivors, some of the future challenges are to add new evidence on the effectiveness of PE on bone health (BMD, accidental falls, and fractures) and on cognitive function [81].

Another important aspect to consider is the safety and the tolerance of PE in this population. In fact, it is plausible that individuals in the advanced stages of the disease may not be able to tolerate the evidence-based exercise prescription. In this context, the published studies have been incomplete in their reporting of adherence to the prescribed FITT programs, thus undermining the feasibility and safety of PE interventions [81,95]. Research is therefore needed to improve the level of specificity for all types of exercise in the prescription of PE to cancer survivors [81,95].

The effects of PE in patients with PCa

Based on the knowledge and given the already widely demonstrated benefits of PE in the healthy population [8], the role of PE is currently being studied both in primary prevention and in all stages of PCa treatment. Preliminary evidence suggests that PE associated with a healthy lifestyle may be able to delay the need for active treatment in men under active surveillance [96] and for advanced metastatic disease [97,98]. Furthermore, PE seems to be a useful strategy to manage the adverse effects of PCa treatments. Recent evidence has demonstrated a positive impact of postoperative pelvic floor muscle training on both short- and medium- or long-term complications of prostatectomy [99], while further studies are needed to clarify its effectiveness when it is started in the preoperative stage [99,100].

A systematic review with meta-analysis (2018) has evidenced that PE significantly reduced the sense of fatigue in men with PCa receiving RT, both alone and with concomitant ADT [101,102].

Furthermore, there is a considerable research on the potential role of PE to counterbalance the numerous side effects of ADT in vulnerable men with PCa. Considering that the life expectancy of patients with PCa has increased, appropriate new strategies aimed at countering the physiological side effects of ADT seem relevant so that they can be devised and recommended.

Recent evidence on this population underlines the benefits of PE on muscle mass and strength, exercise tolerance and physical performance, body composition, and fatigue, while any positive effects on BMD, cardiometabolic risk, and cognitive functions remain unclear [9,94,103–105].

PE that includes aerobic and/or resistance exercise would therefore seem to also benefit PCa patients receiving ADT [104]. Likewise, impact activities such as jumping and high-intensity progressive resistance exercise could also be recommended in this population given positive effect of these activities on bone health and their preventive effects on osteoporosis in healthy individuals [41,106].

Finally, PE that includes balance exercises is recommended for elderly people to reduce the risk of accidental falls [57]. Thus, although there is a lack of evidence in patients with cancer [81,107], it is plausible that this type of exercise may reduce the risk of accidental falls in vulnerable men with PCa.

Therefore, along with aerobic and resistance exercises, which are essential given their ascertained beneficial effects, PCa patients might also benefit from impact activities and neuromotor exercises that include balance, coordination, and dual-task exercises [8,107].

Currently, the WHO claims that one out of four adults do not reach the minimum levels of PE recommended by the guidelines, with higher levels of sedentary behaviors among the older population [108,109].

In addition to this, a cancer diagnosis has a negative effect on PE participation: about 30% of patients report that their habitual level of exercise has decreased since diagnosis, and clinical studies focusing on PE register low recruitment rates [110,111]. In this regard, it is noteworthy that, according to WHO, physical activity comprises any body movement produced by muscle contraction resulting in energy expenditure above a resting level. PE is a more restrictive concept and is defined by planned, organized, and repetitive physical activity aimed at maintaining or enhancing one or more components of physical fitness or a specific health outcome [112]. Thus, there may be several barriers to PE that affect its feasibility and safety.

The main barriers reported by cancer patients concerning PE are the side effects of treatment (such as incontinence for PCa), lack of time, and fatigue [113,114]. Two recent studies conducted on men with PCa showed adherence rates below 50% of the PE levels recommended by guidelines [115,116]. In addition to the above-mentioned barriers, ageing and the presence of comorbidities also act as risk factors for not engaging in regular PE in this population [117].

The effects of lifestyle in patients with PCa

The ACS guidelines provide specific recommendations regarding health behaviors for cancer prevention. In addition to being physically active, these guidelines recommend controlling body weight, consuming a healthy diet, avoiding smoking, and avoiding or limiting alcohol drinking to reduce cancer risk [80].

Overweight and obesity represent lifestyle-related risk factors for mortality of several cancers [118], and excess body weight is associated with approximately 10.9% of cancer cases diagnosed in the United States during 2014 among women and 4.8% of cancer cases among men [119].

Excess adiposity can contribute to a carcinogenesis promotion through several mechanisms: inflammation, oxidative stress, cell proliferation and angiogenesis, inhibition of cell apoptosis, and metastases [120]. In fact, preliminary evidence suggests obesity is associated with higher risk of aggressive PCa [121,122]. Also elevated BMI and weight gain have been associated with PCa incidence, progression and mortality [123–125]. Results from a lifestyle intervention study have demonstrated that weight loss improves insulin sensitivity and hormone metabolism, two mechanisms that contribute to reducing risk of breast cancer incidence and recurrence [126,127]. Furthermore, a multicomponent lifestyle intervention is considered a strategy to prevent obesity and metabolic syndrome in men with PCa receiving ADT [128], and to improve PCa survival outcomes [80,129].

Diet is considered a lifestyle factor that influences PCa risk, acting not only on body weight but also through biological mechanisms [129]. In general, measures are very similar to those recommended by the ACS guidelines for cancer prevention [80,119,130]. According to these guidelines a healthy eating pattern includes foods that are high in nutrients in amounts that help achieve and maintain a healthy body weight. Foods considered healthy include fruits and the dark green, red and orange vegetables, fiber-rich legumes, and whole grains. Red and processed meats, sugar-sweetened beverages, and highly processed foods and refined grain products are considered foods to limit or avoid. [80,130]. In addition to dietary patterns and foods, there are some nutrients that may alter the risk of several cancers. In this regard, limited evidence suggests that calcium and dairy products increase the risk of PCa. A systematic review of 32 studies showed an increased risk of PCa with high intakes of dairy products [131]. In addition, higher doses of calcium (>2000 mg) were associated not only with greater risk of PCa, but also with more aggressive cancer [132].

Several studies reported that smoking is associated with higher risk of PCa progression, including biochemical recurrence, metastasis, hormone-refractory PCa, and PCa-specific mortality [133,134]. A large prospective observational study among 5366 men diagnosed with PCa, with 22 years of follow-up, current smoking prior to diagnosis was associated with an increased risk of PCa mortality and biochemical recurrence [133]. In addition, quitting smoking for at least 10 years results in a PCa-specific mortality risk similar to that of men who never smoked [133]. With regard to alcohol consumption, the recommended dose is no more than 1 alcohol unit/day for women and 2 alcohol units/day for men [80]. A meta-analysis conducted by Zhao et al. (2016) showed a positive association between alcohol drinking and risk of PCa with dose-response relationship [135].

Significance

The lack of evidence on the effectiveness of PE on relevant outcomes for clinical physiotherapy practice, such as accidental falls and fractures, represents the rationale for expanding the research in this area. Although the role of PE aimed at improving bone health is still uncertain, it is plausible that it may have a beneficial effect on the management of ADT side effects in patients with PCa. Thus, PE may have a potential role in counteracting the side effects of ADT by promoting an increase in bone and muscle strength, which can lead to positive effects on the musculoskeletal system. Moreover, since ADT may be continued for many years, the role of PE can be especially relevant in improving physical and physiological parameters, and thus, quality of life. PE targeting bone health should be a multicomponent, long-term, high-intensity program. Nevertheless, it seems that adherence to PE is poor in this population. In this regard, the period immediately following the diagnosis of PCa seems to be a teachable moment to promote PE habits and improve survivorship. As such, the findings from this study may have important applications to PE prescription in patients with PCa receiving ADT.

Purpose

Therefore, this research project has four aims:

1) To conduct a systematic review of the literature on the effectiveness of PE in patients with PCa receiving ADT to prevent bone health (accidental falls and fractures and BMD loss);

2) To conduct a systematic review of the literature on the feasibility and safety of PE programs for bone health prevention in men with PCa receiving ADT;

3) To describe the lifestyle and PE habits of a sample of men newly diagnosed with PCa and to describe their perceived barriers and motivation to change towards healthier behaviors;

4) To assess the feasibility and safety of a multicomponent experimental PE program to prevent accidental falls and fractures in men with PCa treated with ADT and RT.

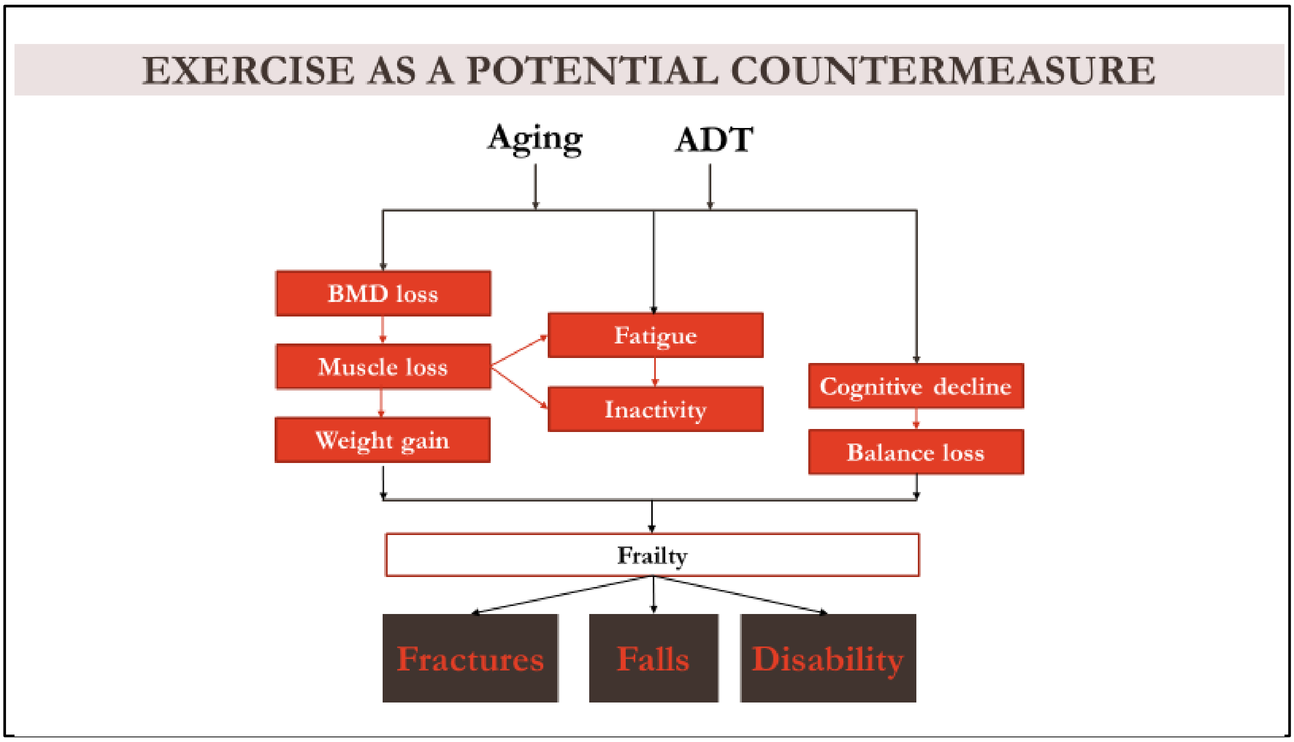
The purpose of my thesis is to extend the current knowledge to arrive at feasible, safe, optimal PE as an integral part of cancer treatment for patients with PCa. If the PE program satisfies these assumptions, its effectiveness in preventing accidental falls and fractures will also be tested in the future.

Four studies were conducted during the 3-year PhD research course (2018-2021). This thesis includes two systematic literature reviews (Chapters II and III), one observational study (Chapter IV), and one protocol of a feasibility pilot study (Chapters V) examining an experimental PE program as a clinically feasible and safe intervention which could impact bone health. The final chapter of this thesis discusses the results of the studies presented and future perspectives.

CHAPTER II

Systematic review of literature one

Physical exercise for bone health in men with prostate cancer receiving androgen deprivation therapy: a systematic review[a]



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Barbara Bressi[1,2], Maribel cagliari[3], Massimiliano Contesini[4], Elisa Mazzini[5], Franco Antonio Mario Bergamaschi[6], Alfredo Moscato[6], Maria Chiara Bassi[7] & Stefania Costi[3,8] .

Affiliations:

[1]PhD Program in Clinical and Experimental Medicine, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Reggio Emilia, Italy.
[2]Physical Medicine and Rehabilitation Unit, Azienda USL–IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[3]Department of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy.
[4]Human Resource Development - Training Radiographers and Radiations Therapist, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[5]Medical Directorate Hospital Network, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[6]Urology and Mininvasive Surgery, Department of General and Specialist Surgeries, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[7]Medical Library, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[8]Scientific Directorate, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.

ABSTRACT

Purpose: Androgen deprivation therapy (ADT) is a treatment used in men with prostate cancer (PCa), however is responsible for many adverse effects, with negative impact on quality of life. ADT causes loss of bone mineral density (BMD) and skeletal muscle mass, alteration of body composition and cognitive function, that altogether lead to increased risk of accidental falls and fractures. This systematic review analyzes the effectiveness of physical exercise (PE) in preventing accidental falls and fractures and reducing the loss of BMD in men with PCa receiving ADT.

Methods: We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library for articles between database inception and September 2, 2020. Eligible studies included randomized controlled trials (RCTs) investigating the effects of exercise on bone health in men with PCa receiving ADT.

Results: Nine RCTs were included. Experimental PE consisted in multicomponent programs that involved aerobic, resistance, impact-loading exercise, and football training. None of the RCTs investigated the risk of accidental falls and fractures, while two trials reported beneficial effects of PE on lumbar spine, hip, and femoral shaft BMD. No further significant difference was detected in the outcomes investigated.

Conclusion: Evidence of the effectiveness of PE to prevent the risk of accidental falls and fractures and BMD loss is lacking. Nevertheless, clinical guidelines recommend PE as a part of the clinical management of men with PCa receiving ADT due to its known numerous health benefits. Research should focus on PE strategies to prevent accidental falls, a clinically relevant outcome in this vulnerable population.

Trial registration: The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, number CRD 42020158444) on 04/28/2020.

Key words: Prostatic neoplasms; Exercise; Accidental falls; Fractures, Bone; Physical therapy modalities; Prevention.

INTRODUCTION

Prostate cancer (PCa) is the most prevalent cancer among men worldwide, with 3.724.658 cases in 2018 [2].

Androgen deprivation therapy (ADT) is currently the standard systemic treatment in patients with metastatic or more aggressive PCa [136]. Often, ADT is used in combination with radiotherapy for localized advanced PCa with the aim to increase survival and control disease progression [136].

However, ADT is responsible for many adverse effects, with a negative impact on quality of life [137].

Apart from the increased risk for cardiovascular events and metabolic syndrome [138,139], ADT also alters the body composition, with loss in skeletal muscle mass that leads to a decrease in muscle strength [46,139]. Also, patients on ADT manifest significant loss of bone mineral density (BMD), which occurs especially within the first year of treatment [40] and is associated with higher osteoporosis rates and risk of fractures [35]. Moreover, ADT seems responsible for cognitive dysfunction, although this finding has not been completely clarified and needs further investigation[140].

It is known that both reduction in muscle strength and cognitive dysfunction are predictors of higher fall rates and hospitalization in older adults [42,141]. Thus, considering the loss of BMD, altogether these side effects of ADT explain the increased risk of accidental falls and fractures in this population [43].

In elderly adults, physical exercise (PE) has been proposed in different modalities as a strategy to produce several health benefits [142]. Recent guidelines addressing elderly adults recommend multicomponent exercise programs, including resistance and neuromotor exercises, as a strategy to reduce the risk of accidental falls [142] as PE can prevent osteoporosis and improves body composition, muscle strength, and cognitive function [142]. Moderate-vigorous intensity programs that include balance exercises seem to be particularly effective to reduce the risk of accidental falls [142].

Initial evidence indicates that in patients with cancer, PE may produce numerous benefits on physical performance, quality of life, and cancer-related fatigue [143]. In patients with PCa receiving ADT, exercise is beneficial to body composition, muscle strength, and physical performance [144–146], while its effects on bone health, cardiometabolic risk, quality of life, and cognitive functions remain uncertain [9,94].

Patients receiving ADT are more exposed to the risk of accidental falls and fractures [35] due to the side effects of this drug. As PE is recommended in healthy elderly adults to prevent these risks and also to prevent bone loss, we hypothesized that PE could be effective in preventing accidental falls and fractures even in men with PCa receiving ADT. Furthermore, recent evidence suggests PE as a strategy to prevent osteoporosis in men receiving ADT when associated with pharmacological therapy [147]. Thus, we conducted this systematic review to search for evidence of the effectiveness of exercise on bone health in this population. Specifically, we searched for randomized controlled trials (RCTs) that implemented PE programs to prevent accidental falls and fractures, and/or to prevent the loss of BMD, in patients with PCa treated with ADT.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [148]. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, number CRD 42020158444).

Search strategy and selection criteria

A systematic review of the literature was performed through sequential, individualized searches in MEDLINE, EMBASE, CINAHL, and the Cochrane Library. We searched for studies published up to September 2, 2020, without filters for study design or language. The search terms and strategies used are reported in Supplementary material Appendix I. Duplicates were removed in EndNote (version X7.5). Also, we performed a manual search in the reference lists of the studies included in this review to find any other relevant citation that may have been missed by the electronic search.

We included RCTs investigating the effects of supervised or unsupervised exercise on bone health in adult individuals with PCa receiving ADT.

Studies were eligible if the experimental intervention consisted of structured PE programs compared to standard care or placebo active control. When exercise was associated with dietary supplements, studies were included if the exercise was clearly the predominant part of the experimental intervention. Furthermore, studies were eligible if they investigated the number of accidental falls or fractures that occurred in a specific timeframe or if they reported data on bone density by dual-energy X-ray absorptiometry (DEXA). Studies focusing on generalized advice and education on the benefit of exercise or studies that collected data on pathological (and not accidental) fractures were excluded.

Data analysis

Two investigators (B.B., M.C.) screened the title and abstract of all the citations retrieved to check their appropriateness related to the purpose of this review. The investigators also retrieved and checked for eligibility the full texts of studies deemed appropriate. Then, two investigators (B.B., S.C.) assessed the eligible studies for their methodological quality according to the Cochrane risk-of-bias tool [149]. In the whole process, any disagreement was resolved by discussion and consensus.

Two investigators (B.B., M.C.) extracted the following data from studies included: authors, year and country, sample size and average age, exclusion criteria, bone outcome measures collected and follow-up duration, general characteristics of the experimental intervention and standard care, drop-out rate. When essential data were missing, the investigators requested them from authors (at least three attempts).

RESULTS

Bibliographic search results

The electronic search yielded 304 citations, duplications excluded. One more citation was retrieved through the manual search, for a total of 305. According to the screening of title and abstract, 269 citations were excluded because they did not focus on the topic under investigation.

Thirty-six full texts were reviewed for eligibility, 27 of which were excluded for the following reasons: three conference abstracts and six study protocols referred to published full-texts already retrieved [150–157]; four studies did not meet inclusion criteria with respect to the outcome, as one measured only pathological fractures [158] and the others did not report data on bone health [157,159,160]; one study did not test a structured PE intervention, focusing instead on patient education [161]; two studies compared different structured PE interventions, without comparison to standard care [162,163]. Finally, eleven studies were also excluded since they reported insufficient data for analysis [164] or were protocols of ongoing studies [165–174]. We contacted the corresponding authors in order to obtain preliminary results (minimum three attempts), but the ones who replied said they had no data to share yet.

Thus, nine published full texts met the inclusion criteria and contributed their data to this review [150–156,175,176]. These full texts accounted for eight study designs, as the two by Uth et al. [154,155] reported data collected at the 3- and 8-month follow-up, respectively, of the same study design and sample (Figure 2.1). Of note, the study by Bjerre et al. [156] included patients with PCa regardless of their treatment with ADT. However, they reported specific data for the subgroup of patients on ADT and these data were considered in this review.

Risk of bias of the included studies

The Cochrane risk-of-bias analysis of the included studies is reported in Figure 2.2. Two studies did not report sufficient information to assess the adequacy of the random sequence generation [154,155,175,177]. Due to the nature of the intervention, seven of the nine included studies did not provide blinding to group assignment for both participants and personnel [150–156,175]. Moreover, four studies did not report enough information to judge blinding of outcome [150–152,175]. Nevertheless, all the included studies were judged at low risk of detection bias since outcome measures were frequently objective. The analytical assessment of the risk of bias for each study included is reported in Supplementary material Appendix II

Figure 2.1 PRISMA Flow Chart of search and study selection process.

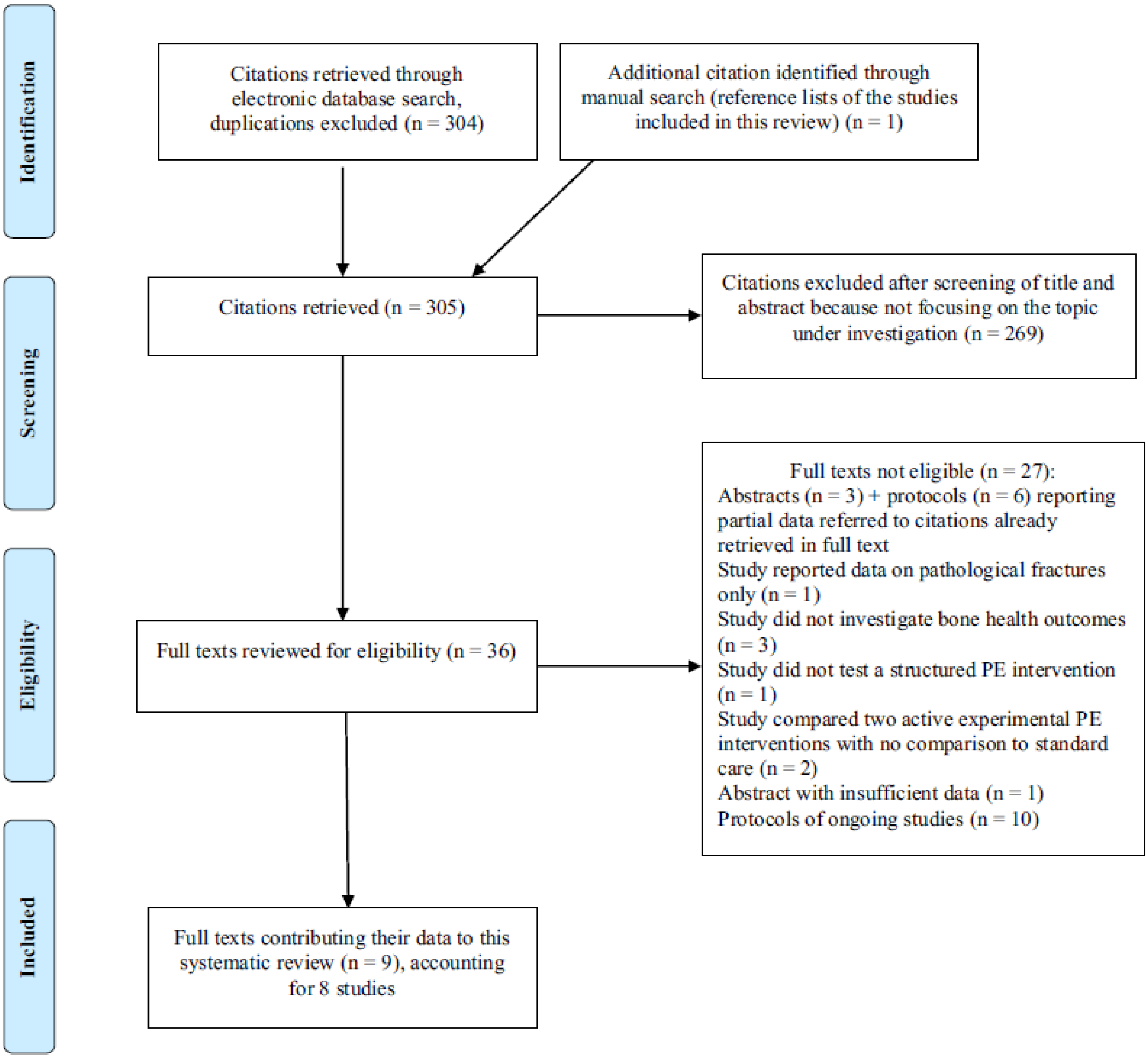


Figure 2.2 Risk-of-bias analysis of RCTs included.

	Random Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cormie et al. (2015)[150]	+	+	−	+	+	+	+
Newton et al. (2019)[151]	+	−	−	+	+	+	+
Taaffe et al. (2019)[152]	+	+	−	+	+	+	+
Nilsen et al. (2015)[153]	+	−	−	+	+	+	+
Uth et al. (2013, 2016)[154,155,177]	?	+	−	+	−	+	+
Bjerre et al. (2019)[156]	+	+	−	+	+	+	+
Winters-Stone et al. (2014)[175]	?	+	−	+	+	+	+
Kim et al. (2018)[176]	+	+	+	+	−	+	+

Study characteristics

Table 2.1 summarizes the characteristics of the studies included in this review. All were RCTs published in the last decade in different continents [150–156,175,176]. All studies allowed for the recruitment of patients treated at several specialized hospitals.

One study was a three-armed RCT comparing two active interventions to one control [151]. For the purposes of this review, we considered both the comparisons. Two studies were cross-over designs and, for this review, we considered data of the first follow-up, before the cross-over, which was scheduled at 6 months for both studies [151,152].

A high drop-out rate (≥ 28%) was registered in two studies [155,175] and equal to 20% in a further one [176], whereas one study did not report this data point for the subgroup of patients receiving ADT [156]. The safety of interventions was assessed by recording the number and type of adverse events. Only two trials reported adverse events related to exercise [153,154]: one partial Achilles tendon rupture [154], two fibula fractures [154], and five minor musculoskeletal injuries [153,154]. Other trials registered generic health issues not related to the PE intervention that occurred both in the experimental and in the control group, such as hospitalization (n=22) [151–153,155,175,176], injury/accident (n=10) [151–153], death (n=4) [151,175], and others (n=4) [150,152–155]. Bjerre et al. [156] analyzed safety outcomes as the number of falls, fractures, and serious adverse events occurring even in the subgroup of patients receiving ADT (respectively n=5, n=1, and n=4), without any further detailed classification.

Participants

The sample size of the eight RCTs selected in this review ranged from 51 to 154 individuals, for a total of 625 participants, of whom 351 were randomized to receive experimental PE and 274 were randomized to receive standard care. The sample was made up of males aged from 66.0 to 70.8 years with local or metastatic PCa receiving ADT.

All the study designs excluded patients with restrictions to PE based on specific assessments (e.g., inability to walk 400 m [150–152], VO^2 max < 35 ml/Kg/min [154,155], pain in the metastatic site associated with activity [154,155]) or based on clinicians' judgement [150–153,156,175,176]. Five studies also excluded patients with musculoskeletal, cardiovascular, and neurological disorders that could inhibit them from exercising [150–155], or patients with contraindications to unsupervised exercise [176]. Further exclusion criteria have been summarized in detail in Table 2.1.

Table 2.1 Characteristics of included studies.

First author (year of publication)	Country	Population			Exclusion criteria	Age (mean ± SD years)			Follow-up (months)	Drop-out rate	Bone outcomes
		EG	CG	Tot.		Tot.	EG	CG			
Cormie et al. (2015)[150]	Australia	32	31	63	Restriction to physical exercise based on clinicians' judgement Musculoskeletal, cardiovascular, neurological disorders Prior exposure to ADT Bone metastasis	68.3*	69.6 (6.5)	67.1 (7.5)	3	13%	aBMD of whole body, lumbar spine (L_2-L_4) femoral neck
Newton et al. (2019)[151]	Australia	57 (RE+IE)	47	154	Restriction to physical exercise based on clinicians' judgement Musculoskeletal, cardiovascular, neurological disorders Current regular resistance exercise Medication that affect bone metabolism Bone metastasis	69.0 (9.0)	68.7 (9.3)	69.1 (8.4)	6	19%	BMD of whole body, total hip, lumbar spine (L_2-L_4), femoral neck, trochanter
		50 (AE+RE)					69.1 (9.4)		6	14%	
Taaffe et al. (2019)[152]	Australia	54	50	104	Restriction to physical exercise based on clinicians' judgement Musculoskeletal, cardiovascular, neurological disorders Current regular resistance or aerobic exercise Prior exposure to ADT Osteoporosis Medication that affect bone metabolism Metastatic disease	68.2*	69.0 (6.3)	67.5 (7.7)	6	18%	BMD of whole body, total hip, lumbar spine
Nilsen et al. (2015)[153]	Norway	28	30	58	Restriction to physical exercise based on clinicians' judgement Musculoskeletal, cardiovascular, neurological disorders Current regular resistance exercise Medication that affect bone metabolism	66.0	66.0 (6.6)	66.0 (5.0)	4	16%	aBMD of whole body, total hip, total lumbar spine, femoral neck, trochanter
Uth et al. (2016)[154]	Denmark	29	28	57	Musculoskeletal, cardiovascular, neurological disorders Current regular resistance exercise Current chemotherapy Osteoporosis Other cancers	67.0	67.1 (7.1)	66.5 (4.9)	3	14%	aBMD of whole body, legs, total hip, lumbar spine, femoral neck, femoral shaft
Uth et al. (2016)[155]									8	28%	
Bjerre et al. (2019)[156]	Denmark	46	41	87	Restriction to physical exercise based on clinicians' judgement Osteoporosis	NR	NR	NR	6	NR	BMD of whole body, total hip, lumbar spine, femoral neck
Winters-Stone et al. (2014)[175]	USA	29	22	51	Restriction to physical exercise based on clinicians' judgement Current regular resistance exercise	70.2	69.9 (9.3)	70.5 (7.8)	12	29%	BMD of total hip, lumbar spine (L_1-L_4), femoral neck, greater trochanter

					Current chemotherapy Osteoporosis Medication that affect bone metabolism Bone metastasis						
Kim et al. (2018)[176]	South Korea	26	25	51	Restriction to physical exercise based on clinicians' judgement Contraindications to unsupervised exercise Current regular resistance exercise Osteoporosis Medication that affect bone metabolism Bone metastasis Other cancers	70.8	70.5 (5.0)	71.0 (5.5)	6	20%	BMD of total hip, lumbar spine (L_1-L_4), femoral neck

Abbreviations: aBMD areal bone mineral density, ADT androgen deprivation therapy, AE aerobic exercise, BMD bone mineral density, CG control group, EG experimental group, IE impact-loading exercise, NR not reported for the subgroup that received ADT, RE resistance exercise, SD standard deviation.
* Estimated values.

Characteristics of control group intervention and the experimental group intervention

Table 2.2 summarizes the characteristics of standard care and experimental PE programs.

The control group intervention consisted of stretching activities [175,176] or educational material [151,156,176], or simply in encouraging patients to maintain their usual level of physical activity [153–155]. Taaffe et al. [152] provided all participants with standard daily supplementation of calcium (1000 mg/day) and vitamin D3 (800 IU/day).

Experimental PE interventions were characterized by multicomponent programs [150–152,154–156,175,176], with only one exception that implemented a single component of PE [153]. In most cases, PE consisted in aerobic exercise (AE) that could also be performed as weight-bearing activities and that was associated with resistance exercise (RE) [150–152,176] and with impact-loading exercise (IE) [152]. Two study designs implemented football training (FT) as experimental PE [154–156]; although the full texts did not report this type of training in detail, it is likely that, by its nature, it included AE and IE, among others (e.g., RE, stretching).

Most experimental interventions were performed in one-hour sessions repeated two or three times a week [150–156,175]. Most of the studies described how the PE components were progressively modulated in terms of intensity, volume, and type of exercise [150–153,175,176]. Although the intensity of FT was not defined, this type of intervention was implemented through an initial warm-up followed by 2 matches lasting 15/20 minutes [154–156]. Uth et al. [154,155] progressively increased the number of matches and the frequency of sessions per week.

Experimental PE were implemented as supervised exercise in clinics [150–152] or in sports facilities [154–156], as a combination of supervised and unsupervised (home-based) sessions [151,153,175], or as unsupervised home-based PE only [176].

Table 2.2 Characteristics of study intervention programs.

First author (year of publication)	Sample	Duration of intervention (months)	EG Component	Experimental PE program	Frequency (times/weeks)	Session duration (min)	Modality		CG
							Group	Single	
Cormie et al. (2015)[150]	EG: 32 CG: 31	3	AE+RE	Supervised: AE: 20-30 min at 70-85% max HR RE: 6-12 RM, 1-4 sets, reps NR Progression: intensity and volume	2	60	x		Standard care
Newton et al. (2019)[151]	EG: 57 CG: 47	6	RE+IE	Supervised: RE: 6-12 RM, 2-4 sets, reps NR Progression: Intensity and volume IE: 3-5 times BW, 2-4 sets, 10 reps. Progression: Set and type of exercise	2	60	x		Printed booklet with information about exercise
				Unsupervised: IE: two to four rotations of skipping (30 s), hopping, leaping, and drop jumping (all 10 times)	2	60		x	
	EG: 50 CG: 47	6	AE+RE	Supervised: RE: 6-12 RM, 2-4 sets, reps NR Progression: Intensity and volume AE: 20-30 min at 60-85 % max HR	2	60	x		
Taaffe et al. (2019)[152]	EG: 54 CG: 50	6	AE+RE+IE	Supervised: AE: 25-40 min of 60-85 % max HR RE: 6-12 RM, 2-4 sets, reps NR Progression: intensity and volume IE: 3·4-5·2 times BW, 2-4 sets, 10 reps Progression: set and type of exercise	3	60	x		Standard care
Nilsen et al. (2015)[153]	EG: 28 CG: 30	4	RE	Supervised: RE: 6-10 RM, 1-3 sets, 10 reps. Progression: volume	2	60	x		Encouraged to maintain their habitual physical activity level and not to initiate strength training
				Unsupervised: Home-based exercise session similar to supervised sessions performed at a moderate intensity	1	60	x	x	
Uth et al. (2016)[154]	EG: 29 CG: 28	3	FT	Supervised: 15 min warm-up (drills, balance, strength exercise) 2-3 sets x 15 min Progression: set and frequency	2-3	45-60	x		Encouraged to maintain their habitual physical activity level
Uth et al. (2016)[155]		8							
Bjerre et al. (2019)[156]	EG: 46 CG: 41	6	FT	Supervised: 20 min warm-up 20 min dribbling, passing, and shooting 20 min of 5–7-a-side football Intensity and progression are NR	2	60	x		15/30-min telephone session covering options for physical activity and free-of-charge rehabilitation delivery by the municipalities and subsequently an email with the same information
Winters-Stone et al. (2014)[175]	EG: 29 CG: 22	12	RE+IE	Supervised: RE upper body: 8-15 RM, 1-2 sets, 8-14 reps. RE lower body: 0-15 % BW, sets NR, 8-12 reps IE: 0-10 % BW, 1-10 sets, 10 reps Progression: Intensity and volume	2	60	x		Performed a series of whole body stretching and relaxation exercises

				Unsupervised: Home-based exercise similar to class session but performed without weighted vests and replacing weights with resistance bands	1	60	x	
Kim et al. (2018)[176]	EG: 26 CG: 25	6	AE+RE	Unsupervised: Core program: Weight-bearing + RE RE: 0-10 % BW, 2-3 sets, 8-15 reps. IE: weight-bearing exercise 11-15 RPE, 3-5 sets, 20-30 min Progression: intensity, volume, and type of exercise Optional program: stabilization/balance exercise + Circuit Resistive Calisthenics (same dose as core program) Stabilization/balance exercise: intensity and volume NR	2-5	NR	NR	Stretching 3-5 times/week (a total of 9 movements); Ten-min telephone sessions (weekly for the first month and at monthly intervals thereafter)

Abbreviations: AE aerobic exercise, BW body weight, CG control group, EG experimental group, FT football training, HR heart rate, IE impact-loading exercise, NR not reported, PE physical exercise, RE resistance exercise, Reps repetitions, RM repetition maximum, RPE rate of perceived exertion, S seconds.

Bone outcomes

Accidental Falls and Fractures

None of the studies selected for this review was designed to analyze the risk of accidental falls and/or fractures as an outcome measure of the effectiveness of experimental PE in reducing those risks. All study designs measured adverse events [150–156,175,176]. The two studies that tested FT also recorded fractures occurring during this kind of intervention to judge its safety due to the increased risk of collisions with other players and falls [154–156]. Although this was not the outcome we were interested in, we underline that all the experimented PE programs were deemed safe [150–156,175,176].

Of note, several studies secondarily collected data on physical function through heterogeneous tests (e.g., Flamingo balance test, sit-to-stand test, etc.) [150,153–155,176]. The proof of effectiveness of experimental PE was demonstrated through the sit-to-stand test [150,153,176], which is valid to measure muscle power of the lower limbs; its validity in predicting accidental falls and fractures in patients with cancer, however, must still be demonstrated [107].

BMD

Table 2.3 reports the results of between-group comparisons of BMD at the various anatomical sites. All the RCTs selected for this review reported data on bone density measured by DEXA at different anatomical sites (Table 2.3). Lumbar spine BMD was collected in all the included studies, while femoral neck BMD was analyzed in seven of them [150,151,153,155,156,175,176]. At the 6-month follow-up, Newton et al. [151] recorded a significant difference between groups for lumbar spine BMD (mean change 0.014 g/cm^2, 95% CI 0.001 to 0.027, p=0.039) and a positive trend for femoral neck BMD (mean change 0.010 g/cm^2, 95% CI 0.000 to 0.020, p=0.050), in favour of the experimental resistance and impact-loading PE compared to control group. No further significant difference was detected by any of the studies in these outcome measures. Of note, a per-protocol analysis performed by Winters-Stone et al. [175] at the level of single lumbar vertebra reported a significant difference in BMD only for L_4 (p=0.03), in favour of experimental PE.

Total hip BMD was measured by seven study designs [151–153,155,156,175,176], with significant differences recorded only by Uth et al. [155] on both hips at the 8-month follow-up (right: 0.015 g/cm^2, 95% CI 0.003 to 0.027, p=0.015; left: 0.017 g/cm^2, 95% CI 0.002 to 0.032, p=0.030). This study was the only one that collected data on BMD at the femoral shaft of both legs, recording a difference in favour of experimental PE on both sides (right: 0.018 g/cm^2, 95% CI 0.004 to 0.032, p=0.016; left: 0.024 g/cm^2, 95% CI 0.005 to 0.044, p=0.015) [155].

No further statistically significant difference was registered for BMD at any further anatomical site examined, such as the whole body [150–154,156], trochanter [151,153,175], or legs [154].
Considering the almost total absence of data in favour of PE with respect to this outcome, which was collected in various anatomical sites, we deemed it inappropriate to carry out a meta-analysis.

Table 2.3 Between-group comparisons for BMD.

First author (year of publication)	Follow-up (months)	BMD outcome	Mean change between groups (g/cm^2)	95% CI	*p*-value
Cormie et al. (2015)[150]	3	Whole body	-0.002*	-0.013 to 0.009	0.692
		Lumbar spine	-0.009*	-0.029 to 0.012	0.410
		Femoral neck	0.000*	-0.025 to 0.024	0.987
Newton et al. (2019)[151]	6 (RE+IE)	Whole body	0.005*	-0.002 to 0.011	0.174
		Total hip	0.007*	-0.002 to 0.016	0.128
		Lumbar spine	0.014*	0.001 to 0.027	0.039
		Femoral neck	0.010*	0.000 to 0.020	0.050
		Trochanter	-0.003*	-0.010 to 0.004	0.449
	6 (AE+RE)	Whole body	0.003*	-0.007 to 0.0012	0.614
		Total hip	0.001*	-0.009 to 0.011	0.807
		Lumbar spine	0.004*	-0.009 to 0.017	0.525
		Femoral neck	-0.003*	-0.014 to 0.008	0.571
		Trochanter	-0.002*	-0.01 to 0.007	0.699
Taaffe et al. (2019)[152]	6	Whole body	NR	NR	0.827
		Total hip	NR	NR	0.848
		Lumbar spine	NR	NR	0.111
Nilsen et al. (2015)[153]	4	Whole body	0.00*	-0.02 to 0.01	0.520
		Total hip	0.00*	-0.01 to 0.01	0.690
		Total lumbar spine	0.00*	-0.02 to 0.01	0.847
		Femoral neck	0.00*	-0.02 to 0.01	0.467
		Trochanter	0.00*	-0.01 to 0.00	0.221
Uth et al. (2016)[154]	3	Whole body	0.01	-0.00 to 0.01	0.188
		Legs	0.00	-0.00 to 0.01	0.336
Uth et al. (2016)[155]	8	Total hip	R: 0.015	0.003 to 0.027	0.015
			L: 0.017	0.002 to 0.032	0.030
		Lumbar spine	0.028	-0.010 to 0.065	0.144
		Femoral neck	R: 0.015	-0.002 to 0.031	0.078
			L: 0.015	-0.01 to 0.032	0.072
		Femoral shaft	R: 0.018	0.004 to 0.032	0.016
			L: 0.024	0·005 to 0·044	0.015
Bjerre et al. (2019)[156]	6	Whole body	0.005	-0.007 to 0.017	0.40
		Total hip	-0.009*	-0.033 to 0.014	0.43
		Lumbar spine	0.0017*	-0.019 to 0.053	0.34
		Femoral neck	0.007*	-0.009 to 0.023	0.39
Winters-Stone et al. (2014)[175]	12	Total hip	NR	NR	0.37
		Lumbar spine	NR	NR	0.47
		Femoral neck	NR	NR	0.77
		Greater trochanter	NR	NR	0.58
Kim et al. (2018)[176]	6	Total hip	NR	NR	0.727
		Lumbar spine	NR	NR	0.756
		Femoral neck	NR	NR	0.888

Abbreviations: AE aerobic exercise, BMD bone mineral density, CI confidence intervals, IE impact-loading exercise, L left, NR not reported, R right, RE resistance exercise.
* Analyses adjusted for baseline values.

Further results: Bone turnover markers

Six study designs also assessed several bone turnover markers (BTMs) such as markers of bone formation (alkaline phosphatase, procollagen type 1 amino-terminal propeptide and osteocalcin) or markers of bone resorption (C-terminal telopeptide of type I collagen, N-terminal telopeptide of type I collagen) [150–152,154,155,175,176].

At the 3-month follow-up, Uth et al. [154,155] registered a statistically significant difference in favour of experimental PE for the markers of bone formation procollagen type 1 amino-terminal propeptide (36.6 µg/L, 95% CI 10.4 to 62.8, *p*=0.008) and osteocalcin (8.6 µg/L, 95% CI 3.3 to 13.8, *p*=0.002), but this result was not confirmed at the subsequent 8-month follow-up.

DISCUSSION

The aim of this systematic review was to summarize the evidence regarding the effectiveness of PE programs in reducing the risk of accidental falls and fractures, as a clinically relevant outcome in the PCa patient population.

Despite the strong existing evidence proving accelerated bone loss, additional muscle weakness, and cognitive dysfunction caused by ADT [140,178] and the benefits of PE in reducing the risk of accidental falls in the healthy elderly population [142], no study has investigated the effects of exercise on these clinically relevant endpoints in PCa patients.

Furthermore, the effectiveness of PE in lessening or preventing the loss of BMD in this population is still uncertain due to the inconsistent results yielded by this systematic review. In particular, only two studies suggested that multicomponent PE, in particular resistance and impact-loading exercise or football training, may help achieve this outcome [151,155]. These positive results could be explained by the longer period of training [151], as a minimum of 6–8 months is required to achieve bone remodeling [41], or by the high number of accelerations and decelerations, and change of direction typically observed during the football training [155]. These characteristics of the PE intervention could provide sufficient bone-loading forces and osteogenic stimulus. However, both these study designs were affected by a certain degree of risk of bias. Therefore, although BMD was measured objectively, their results should be interpreted with caution.

Thus, to date, evidence of the beneficial effects of PE on bone health in men with PCa treated with ADT is still lacking, even though PE is beneficial in the healthy elderly for the same outcome [142].

The incidence of osteoporotic fractures increases with age, and it is estimated that more than 8.9 million osteoporotic fractures occur annually worldwide [179,180]. In men over the age of 75, the most frequent site of fracture is the hip, the principal risk factor being low BMD [181]. Moreover, more than 30% of community-dwelling older adults over the age of 75 fall every year [182], leading to fractures, hospitalizations, and admission to nursing homes [183].

Therefore, the risk of falls in older adults increases morbidity, mortality, and financial burden for societies [184]. Indeed, the costs associated with fragility fractures account for €37 billion/year in

Europe and are expected to increase [179], whereas in the USA, the overall number of healthy years of life lost (DALY) due to hip fractures is roughly 17.660 [185].

Considering the progressive ageing of the population, recent guidelines suggest that future research should identify individuals at increased risk of fracture, to whom fracture prevention strategies should be targeted [186] in order to contain the increase in costs associated with this event [187]. We think that patients with PCa receiving ADT are among those individuals because the side effects they have affect bone and lead to double the healthcare cost per person [188]. Moreover, as fall prevention programs are recommended to the elderly in general, as community-dwelling adults with cancer have greater accidental fall rates than do healthy elderly individuals, and as patients undergoing active treatment are even more at risk [189], it seems logical to expect that the beneficial effects of PE would be greater in patients with PCa receiving ADT compared to healthy elderly individuals.

However, this systematic review demonstrated an almost complete lack of studies supporting this. Not only have clinically relevant outcomes never been investigated, but few of the RCTs included were powered to detect the effects of PE on BMD [151,152,175,176].

We must say, however, that our review was limited to collecting evidence on PE. As we did not consider other types of interventions, such as nutritional and educational programs that could help to prevent accidental falls and fractures, we cannot rule out that an evidence-based intervention different from stand-alone PE could be successfully applied. Furthermore, ten protocols of ongoing studies were retrieved by our search strategy; it is therefore very likely that in the next few years the conclusion drawn today, thanks to this extensive review conducted with rigorous methodology, will be outdated.

A final consideration regards the type of PE programs tested in the studies included in this review: most combined different exercise modalities, such as resistance, weight-bearing endurance, and impact loading exercises, as recommended to provide benefits to bone health [41]. Moreover, PE programs were of moderate-high intensity in all cases, suggesting that, according to the evidence and expertise, low-impact exercise may have no effect on BMD [41]. Despite this, the PE programs did not produce the desired result on bone mass. This may be due to the insufficient power of some of the included studies, or it may be due to poor adherence to treatment, which is always an issue in studies involving lifestyle changes [10]. Poor adherence to treatment means that the expected dose of exercise is not achieved by participants. Thus, it can be difficult to determine the effect of the exercise on the outcomes of interest. It could also be that, however intense the program, PE may not be sufficient to counteract the loss of bone mass induced by ageing and ADT.

Thus, to conclude, experts recommend exercise as part of the treatment regimen of patients with cancer thanks to its large number of health benefits [9]. This review suggests that there is still no strong evidence to support this choice to prevent bone density loss in patients with PCa receiving ADT, according to recent literature [144,147]. However, since exercise is an effective strategy to produce a large number of health benefits, future research should investigate the effects of PE to prevent the risk of accidental falls in this population, which is a clinically relevant outcome. For this purpose, PE should include coordination and balance exercises as well as muscle-strengthening activities. Evidence is needed regarding more precise training components, dose, and progression of exercise to prevent falls.

Compliance with Ethical Standards

Funding

No funding was received to support the publishing of this study. The corresponding author had full access to all the data and had final responsibility to submit for publication. The authors agree to allow the journal to review data if requested.

Conflict of interest/competing interest

The authors declare that they have no conflicts of interest.

SUPPLEMENTARY MATERIALS

Appendix I - Research strategies

Ovid Medline on 9/02/2020
#1 "Androgen Antagonists"[Mesh] OR "Gonadotropin-Releasing Hormone"[Mesh]
#2 hormone* OR androgen OR androgen deprivation therapy
#3 #1 OR #2
#4 "Prostatic Neoplasms"[Mesh]
#5 prostat* AND (cancer OR tumor OR neoplasm)
#6 #4 OR #5
#7 "Exercise"[Mesh]
#8 "Physical Therapy Modalities"[Mesh]
#9 exercise* OR physical activit* OR physical therap*
#10 #7 OR #8 OR #9
#11 #3 AND #6 AND #10
Embase on 9/02/2020
#1. hormone*:ab,ti OR androgen:ab,ti OR 'androgen deprivation therapy':ab,ti
#2. 'antiandrogen'/exp/mj OR 'gonadorelin derivative'/exp/mj
#3. #1 OR #2
#4. prostat*:ab,ti AND (cancer:ab,ti OR tumor:ab,ti OR neoplasm:ab,ti)
#5. 'prostate tumor'/exp/mj
#6. #4 OR #5
#7. exercise*:ab,ti OR 'physical activit*':ab,ti OR 'physical therap*':ab,ti
#8. 'exercise'/exp/mj OR 'physiotherapy'/exp/mj
#9. #7 OR #8

#10. #3 AND #6 AND #9
CINAHL on 9/02/2020
S1 hormone* OR androgen OR androgen deprivation therapy
S2 (MH "Androgen Antagonists")
S3 (MH "Gonadorelin")
S4 prostat* AND (cancer OR tumor OR neoplasm)
S5 (MH "Prostatic Neoplasms")
S6 (MH "Exercise")
S7 (MH "Physical Therapy")
S8 exercise* OR physical activit* OR physical therap*
S9 S1 OR S2 OR S3
S10 S4 OR S5
S11 S6 OR S7 OR S8
S12 S9 AND S10 AND S11
Cochrane Library on 9/02/2020
#1 MeSH descriptor: [Androgen Antagonists] explode all trees
#2 MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees
#3 (hormone* OR androgen OR androgen deprivation therapy):ti,ab,kw
#4 #1 or #2 or #3
#5 MeSH descriptor: [Prostatic Neoplasms] explode all trees
#6 (prostat* AND (cancer OR tumor OR neoplasm)):ti,ab,kw
#7 #5 or #6
#8 MeSH descriptor: [Exercise] explode all trees
#9 MeSH descriptor: [Physical Therapy Modalities] explode all trees
#10 (exercise* OR physical activit* OR physical therap*):ti,ab,kw
#11 #8 or #9 or #10
#12 #4 and #7 and #11

Appendix II - The analytical assessment of the risk of bias for each study included.

Item	Authors' judgement	Description
Cormie et al (2015)[150]		
Sequence generation	Low risk	Quote: "Participants were randomised in an allocation ratio of 1:1 using a random assignment computer program".
Allocation concealment	Low risk	Quote: "The project coordinator and the exercise physiologists involved in assigning participants to groups were 'blinded' to the allocation sequence"
Blinding of participants and personnel	High risk	The authors do not specify this aspect. Comment: probably not done.
Blinding of outcome assessment	Low risk	The authors do not specify this aspect. Comment: outcomes considered in this study and extracted for our review (BMD) are not likely to be influenced by lack of blinding.
Incomplete outcome data	Low risk	Quote: "An intention-to-treat approach was used for all analyses using maximum likelihood imputation of missing values (expectation maximization)"
Selective reporting	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	Study appears to be free of other sources of bias.
Newton et al (2019)[151]		
Sequence generation	Low risk	Quote: "patients were randomly allocated by computer random assignment".
Allocation concealment	High risk	The authors do not specify this aspect. Comment: probably not done.

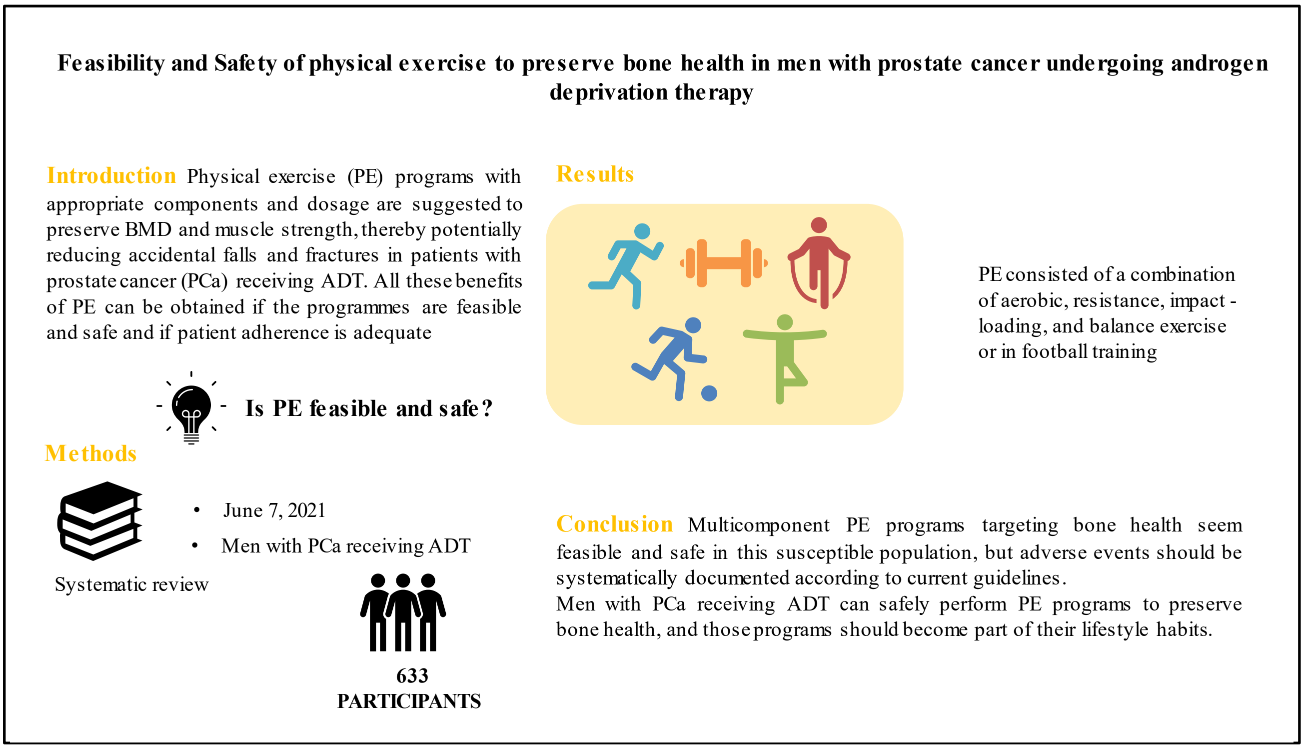
Blinding of participants and personnel	High risk	The authors do not specify this aspect. Comment: probably not done.
Blinding of outcome assessment	Low risk	The authors do not specify this aspect. Comment: outcomes considered in this study and extracted for our review (BMD) are not likely to be influenced by lack of blinding.
Incomplete outcome data	Low risk	Quote: “An intention-to-treat approach was used for all analyzes using maximum likelihood imputation of missing values (expectation maximization)”.
Selective reporting	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	Study appears to be free of other sources of bias.
Taaffe et al (2019)[152]		
Sequence generation	Low risk	Quote: “104 men were randomly assigned using a computer random assignment program”.
Allocation concealment	Low risk	Quote: “This was a single-blinded randomized controlled trail (RCT; investigators and testing personnel blinded to group allocation)”.
Blinding of participants and personnel	High risk	The authors do not specify this aspect. Comment: probably not done.
Blinding of outcome assessment	Low risk	The authors do not specify this aspect. Comment: outcomes considered in this study and extracted for our review (BMD) are not likely to be influenced by lack of blinding.
Incomplete outcome data	Low risk	Quote: “intention-to-treat was used for analyses of primary and secondary endpoints using maximum-likelihood imputation of missing values (expectation maximization)”.
Selective reporting	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
Nilsen et al (2015)[153]		
Sequence generation	Low risk	Quote: “randomization was computerized in a 1:1 ratio by the staff at the clinical research office at Oslo University Hospital”.
Allocation concealment	High risk	The authors do not specify this aspect. Comment: probably not done.
Blinding of participants and personnel	High risk	The authors do not specify this aspect. Comment: probably not done.
Blinding of outcome assessment	Low risk	Quote: “personnel performing DXA scans were blinded to group allocation”.
Incomplete outcome data	Low risk	Quote: “missing data were imputed by an intention-to-treat approach using the last observation carried forward”.
Selective reporting	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	The study appears to be free of other sources of bias.
Uth et al (2016, 2013)[154,155,177]		
Sequence generation	Unclear	Quote: “after successful completion of all baseline assessments participants are randomized 1:1 to the soccer intervention or control group”. Comment: insufficient to be confident that the allocation sequence was genuinely randomized.
Allocation concealment	Low risk	Quote: “The randomization process will be conducted by a research consultant at the Copenhagen Trial Unit who has no other involvement in the study”.
Blinding of participants and personnel	High risk	Quote: “blinding of patients and soccer instructors in this kind of study is not possible”. Comment: not done.
Blinding of outcome assessment	Low risk	Quote: “at the termination of the study a statistician blinded to treatment assignment will perform all analyses before disclosing any study outcome data to the study coordinator and researchers involved in the study”.
Incomplete outcome data	High risk	Quote: “Change scores are calculated only on data from participants assessed at both baseline and at 12 weeks”. Comment: all analyses were conducted per protocol.
Selective reporting	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Bjerre et al (2019)[156]		
Sequence generation	Low risk	Quote: "Patients were randomly allocated in two groups according to a computer-generated list of a number" Comment: insufficient to be confident that the allocation sequence was genuinely randomized.
Allocation concealment	Low risk	Quote: "The allocation was concealed from trial personnel as the statistician received a password-protected email from the trial management system (easyTrial®) with an upload function for the allocation sequence".
Blinding of participants and personnel	High risk	Quote: "Given the nature of the intervention, neither participants nor coaches were blinded" Comment: not done.
Blinding of outcome assessment	Low risk	Quote: "blinding was implemented for objective outcome, so personnel performing assessment had no information on the group allocation"
Incomplete outcome data	Low risk	Quote: "The analyses were performed as described for the ITT population".
Selective reporting	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	Study appears to be free of other sources of bias.
Winters-Stone et al (2014)[175]		
Sequence generation	Unclear	Quote: "we conducted a 12-month single-blind randomized controlled trial comparing two parallel groups". Comment: insufficient to be confident that the allocation sequence was genuinely randomized.
Allocation concealment	Low risk	Quote: "trained technicians blinded to group assignment".
Blinding of participants and personnel	High risk	The authors do not specify this aspect. Comment: probably not done.
Blinding of outcome assessment	Low risk	The authors do not specify this aspect Comment: outcomes considered in this study and extracted for our review (BMD) are not likely to be influenced by lack of blinding
Incomplete outcome data	Low risk	Quote: "data were initially analyzed using an intention-to-treat (ITT) approach via Hierarchical Linear Modeling keeping each participant within his originally assigned group and regardless of missing data".
Selective reporting	Low risk	All prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Kim et al (2018)[176]		
Sequence generation	Low risk	Quote: "A block randomization (block size 4) procedure, using computer-generated randomization numbers".
Allocation concealment	Low risk	Quote: "group assignments were placed in sealed, sequentially numbered envelopes and opened by the participants".
Blinding of participants and personnel	Low risk	Quote: "group assignments were placed in sealed, sequentially numbered envelopes and opened by the participants, who were blind to group assignment (they were informed only that they would be given 1 of 2 types of exercise)".
Blinding of outcome assessment	Low risk	Quote: "licensed technicians blind to study groups measured BMD by dual-energy absorptiometry using…".
Incomplete outcome data	High risk	Quote: "All analyses were conducted per protocol".
Selective reporting	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	Study appears to be free of other sources of bias.

CHAPTER III

Systematic review of literature two

Feasibility and safety of physical exercise to preserve bone health in men with prostate cancer receiving androgen deprivation therapy: a systematic review[b]



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[b] Preprint version of the manuscript accepted for publication by *Physical therapy & Rehabilitation Journal*.

Maribel cagliari[1*], Barbara Bressi[2*], Maria Chiara Bassi[3], Stefania Fugazzaro[4], Giuseppe Prati[5], Cinzia Iotti[6] & Stefania Costi[7]. *The first two authors (MC and BB) equally contributed to this work.

Affiliations:

[1]Department of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, 41121, Modena, Italy. Viale Umberto I, 50, 42123 Reggio Emilia, Italy.
[2]PhD Program in Clinical and Experimental Medicine, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Reggio Emilia, Italy. Department of Neuromotor Physiopathology and Rehabilitation Medicine, Physical Medicine and Rehabilitation Unit. Azienda USL–IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[3]Medical Library. Azienda USL–IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[4]Department of Neuromotor Physiopathology and Rehabilitation Medicine, Physical Medicine and Rehabilitation Unit. Azienda USL–IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[5]Department of Oncology and Advanced Technologies, Oncology Unit. Azienda USL–IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[6]Department of Oncology and Advanced Technologies, Radiotherapy Unit. Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[7]Scientific Directorate. Azienda USL–IRCCS di Reggio Emilia. Department of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, Modena, 41124, Italy.

ABSTRACT

Objective: Men with prostate cancer (PCa) receiving androgen deprivation therapy (ADT) experience the loss of bone mineral density (BMD) and lean body mass, which can increase their risk of falls and fractures. Physical exercise (PE) programs with appropriate components and dosage are suggested to preserve BMD and muscle strength, thereby potentially reducing accidental falls and fractures and associated morbidity and mortality. However, these benefits can be obtained if PE programs are feasible and safe and if patient adherence is adequate. This systematic review investigates the feasibility and safety of PE programs aimed at preventing the risk of accidental falls and fractures and BMD loss in men with PCa receiving ADT.

Methods: We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library, from database inception to June 7, 2021. We included randomized controlled trials that analyzed the feasibility and safety of experimental PE programs targeting bone health in men with PCa receiving ADT. Two reviewers independently selected the studies, assessed their methodological quality, and extracted the data. PE feasibility was measured through recruitment, retention, and adherence rates. PE safety was measured through the number, type, and severity of adverse events. Furthermore, the components, setting, intensity, frequency, and duration of PE programs were extracted.

Results: Ten studies were included, with a total of 633 participants. PE consisted of a combination of aerobic, resistance, and impact-loading exercise or in football training. PE is feasible in men with prostate cancer receiving ADT, although football training should be prescribed with caution for safety reasons.

Conclusions: Multicomponent PE programs targeting bone health seem feasible and safe in this population, but adverse events should be systematically documented according to current guidelines.

Impact statement: Men with PCa receiving ADT can safely perform PE programs to preserve bone health, and those programs should become part of their lifestyle habits.

INTRODUCTION

Prostate cancer (PCa) is the most diagnosed cancer among men worldwide [3], and androgen deprivation therapy (ADT) is the first line of treatment in metastatic or advanced stages of this disease [136]. Nevertheless, ADT causes numerous side effects that can worsen the patient's quality of life [5], such as an increase in cardiovascular disease and metabolic syndrome [46,138] and the loss of bone mineral density (BMD) and of muscle strength [38,190]. These musculoskeletal alterations contribute to sarcopenia, osteoporosis, and frailty [191], which are predictors of accidental falls and fractures in this population [34,36,43], with a significant impact on health-related quality of life, hospitalization, and mortality [44].

As exercise is well tolerated and safe in cancer survivors [192], preliminary evidence supports the introduction of physical exercise (PE) programs to improve the clinical and functional outcomes in this population [193].

More specifically, in men with PCa treated with ADT, PE has the potential to reduce several of the side effects of ADT, such as the loss of muscle strength, muscle mass, and physical function [144]. Moreover, PE programs specifically targeting bone health could preserve BMD [41]. Altogether, these outcomes may also reduce the risk of accidental falls and fractures, although this effect must still be proven [194]. However, in order to produce benefits on the musculoskeletal system, PE should be performed over the long term and at the appropriate dosage [41]. In this respect, a trend toward becoming less physically active has been documented in older adults [195], and several factors may affect patients' long-term adherence to the prescribed exercise regimen, such as the side effects of cancer treatments [113]. In fact, only 41.9% of men with PCa perform the recommended amount of PE, with greater inactivity for individuals treated with ADT [116], whose adherence to experimental PE has recently been estimated to be as low as 30-40% [95]. However, adherence to PE may increase when appropriate and acceptable exercise modalities are proposed [195]. Thus, although adequate PE programs for men with PCa receiving ADT have the potential to preserve BMD and muscle strength, thereby theoretically reducing the risk of accidental falls and fractures [194], this potential cannot be reached if these programs are not sufficiently feasible and safe.

Therefore, this systematic review aimed to investigate the feasibility and safety of PE targeting bone health to prevent BMD loss and accidental falls and fractures in individuals with PCa undergoing ADT. We also aimed to describe the type of PE (components, setting, intensity, frequency, duration) that can be implemented to preserve bone health in this population.

METHODS

This systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [148]. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, number CRD42020163416).

Data sources and searches

A comprehensive search was conducted on MEDLINE, EMBASE, CINAHL, and the Cochrane Library, from their inception until June 7, 2021. The search strategy included terms related to exercise, prostatic neoplasms, androgen antagonists, and associated synonyms (the full search strategy is presented as Supplementary material Appendix I of the Chapter II).

Hand searching of reference lists of the included original studies was undertaken, and the authors of published protocols were contacted to ask for any preliminary results.

Study selection

We included randomized controlled trials (RCTs) that met the following eligibility criteria: Participants: men with PCa undergoing ADT; Intervention: supervised and/or unsupervised PE programs targeting bone health to prevent BMD loss and accidental falls and fractures; Comparison: standard care alone or with placebo; Outcome: feasibility and safety of an experimental PE program. Feasibility was estimated based on recruitment and retention rates and on the patients' adherence to the experimental interventions [196]. The recruitment rate was calculated as the ratio between randomized participants and individuals assessed for eligibility, and the retention rate was calculated as the ratio between the participants that completed the study and those randomized. Patients' adherence to the experimental intervention was calculated as the ratio between the number of PE sessions attended and those planned.

Safety was estimated based on the number and type of adverse events (AEs) reported in the original studies. For the purposes of this systematic review, an AE is any unfavorable symptom or disease that occurred that may or may not be considered related to the intervention experimented (adapted from CTCAE Version 5.0) [197].

We excluded studies where PE was not the key part of the experimental intervention, i.e., any trial focusing chiefly on nutritional, educational, and/or counseling activities.

Data extraction and quality assessment

Two investigators (B.B., M.C.) screened the title and abstract of the records retrieved and reviewed the full texts using predetermined eligibility criteria. Any disagreement was resolved by discussion and consensus.

Two reviewers (B.B., M.C.) independently assessed the quality of the included studies using the Physiotherapy Evidence Database (PEDro) score [198], which is an 11-item checklist to assess the internal validity of an RCT. Each trial is scored out of 10, where a score ≥ 9 corresponds to excellent quality, a score from 6 to 8 corresponds to good quality, a score from 4 to 5 corresponds to fair quality, and a score < 4 corresponds to poor quality [199]. Disagreements were resolved by consensus with a third reviewer (S.C). A priori, we decided not to exclude studies from the analyses based on the quality assessment.

Data synthesis and analysis

Two investigators (B.B, M.C) independently extracted the following data from the included studies: inclusion criteria for participants and sample size, characteristics of the PE program (setting, type, frequency, intensity, modality), supplementary intervention (nutrition, education, counselling, etc.), comparisons (standard care and placebo, if any), feasibility outcomes (recruitment, retention, and adherence rates), safety outcomes (number, type, and severity of adverse events related or unrelated to the intervention), efficacy outcomes (number of falls and fractures and BMD value), and follow-up duration. A detailed description of each PE component was collected. In the case of missing data, the corresponding authors were contacted (at least three attempts) to obtain the desired information.

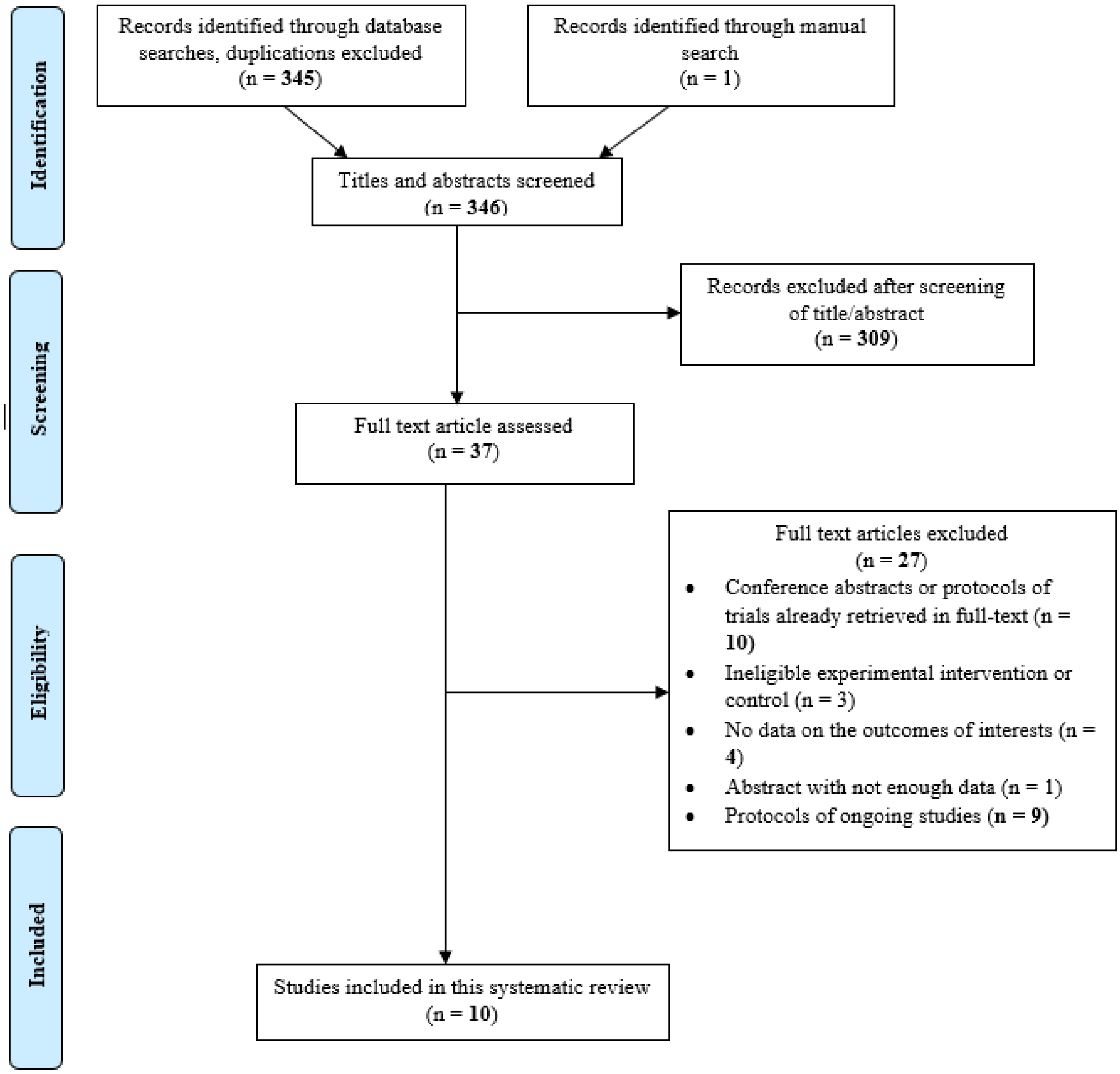
RESULTS

Study selection

The electronic search strategy identified 345 records, excluding duplicates. Through manual searching, we retrieved one more record, for a total of 346. We excluded 309 records based on their title or abstract, assessed the remaining 37 records in full text, and excluded 27 of them for the following reasons: three conference abstracts [200–202] and seven study protocols [169,177,203–207] were duplicates of full texts retrieved [105,150,176,151–157,175]; one study design experimented an intervention chiefly focusing on education [161], and two others compared different active intervention arms [162,163]; four studies did not report data regarding the outcomes of interest, i.e., they did not report any measure of feasibility or safety of PE [156–158,160]. Further, ten studies were excluded because they reported insufficient data for analysis [164] or were protocols of ongoing, unpublished studies [165–168,170–174]. We contacted the authors to collect any preliminary results (minimum three attempts), but they had no data to share yet.

Therefore, ten studies met the inclusion criteria [105,150–155,175,176,208], providing data from nine RCT designs, one of which yielding two published studies [154,155] reporting data collected on the same sample at two different follow-ups (Figure 3.1).

Figure 3.1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of search and study selection.



Quality assessment

The quality of the RCTs included is reported in Table 3.1. Blinding of participants and therapists was not possible due to the type of intervention. All the included studies reported random allocation, similar groups at baseline, differences between groups, and point estimate variability. Most of the included studies reported the intention-to-treat analysis [105,150–153,175], and five of the included studies reported concealed allocation [150,153–155,176], adequate follow-up (>85%) [105,150,154,175,208], and blinding of assessors [105,152,153,175,176]. Overall, seven studies were deemed as good quality [105,150,152–154,175,176] and three as fair [150,155,208]. The two published studies by Uth et al. yielded different PEDro scores due to the lower dropout rate at the 3-month follow-up [154] compared to the dropout rate at the 8-month follow-up [155].

Characteristics of the studies

The characteristics of the RCTs included in this review are shown in Table 3.2. The studies, published between 2014 and 2021, were conducted in Europe [153–155], Australia [105,150–152,208], the USA [175], and Asia [176], and promoted by university hospitals [150–152,176,208] or specialized prostate cancer centers [105,151,154,155]. Two were cross-over designs [151,152]; for the purposes of this review, we considered the data of the first follow-up, before the switch of the treatments, which in both cases was fixed at 6 months. As one RCT compared two active interventions with one control (impact loading plus resistance exercise vs control, and aerobic plus resistance exercise vs control), we considered both the comparisons for the purposes of this review [151]. The follow-up period varied from six weeks [208] to twelve months [105,175,208] after the baseline assessment. All the included studies investigated the effectiveness of exercise to prevent BMD loss; none registered accidental falls and fractures.

Table 3.1 PEDro score of the included studies.

Study	Random allocation	Concealed allocation	Groups similar at Baseline	Participant blinding	Therapist blinding	Assessor blinding	<15% dropouts	Intention-to-treat analysis	Between difference reported	Point estimate and variability reported	Total (0 to 10)
Dalla Via et al (2021)[105]	Y	N	Y	N	N	N	Y	Y	Y	Y	7
Cormie et al (2015)[150]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Newton et al (2019)[151]	Y	N	Y	N	N	N	N	Y	Y	Y	5
Taffee et al (2019)[152]	Y	N	Y	N	N	Y	N	Y	Y	Y	6
Nilsen et al (2015)[153]	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Uth et al (2016)[154]	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Uth et al (2016)[155]	Y	Y	Y	N	N	N	N	N	Y	Y	5
Winters-Stone et al (2014)[175]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Kim et al (2018)[176]	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Lam et al (2020)[208]	Y	N	Y	N	N	N	Y	N	Y	Y	5

Abbreviations: Y, yes; N, no.

Participants

The RCTs included 633 men with local or metastatic PCa undergoing ADT whose average age ranged from 66.0 to 71.0 years (Table 3.2). The sample size ranged from 25 to 154 participants. Overall, 352 men were allocated to experimental PE and 281 to the control group.

Five studies [105,150,154,155,175,176] reported the average time from diagnosis of PCa to enrolment, ranging from 15 to 79 months in participants allocated to experimental PE and from 10 to 76 months in participants allocated to the control group. Participants had been previously treated for cancer by prostatectomy [105,150,152,154,155,176], radiation therapy [105,150,153–155,175,176,208], and/or chemotherapy [105,150,175]. Concomitant cancer treatments were generally allowed, and in some cases, ADT associated with radiation therapy was documented during the participation in the trial [105,150–152]. Only five studies [105,153–155,176,208] reported data on cancer stage, which ranged from stage I to IV according to the TNM classification.

The most frequent exclusion criteria to participation were:

- bone metastasis [150,151,175,176]
- osteoporosis [152–155,175,176]
- previous treatment with ADT [150,152,208]

Table 3.2 Study characteristics.

Study	Country	Participants	Main exclusion criteria	Intervention	Outcome measures
Della Via et al (2021)[105]	Australia	• Local and metastatic PCa treated with ADT • n° tot = 70 IG = 34; CG = 36 • Mean age (year) = 71.0 (range: 50-85) • Time on ADT, Mean (IQR) IG = 8.0 mths (4.0–22.0) CG = 13.0 mths (8.0-24.0)		IG = Supervised and unsupervised resistance exercise training plus weight-bearing impact exercise combined with multi-nutrient supplementation CG = Standard care	• BMD = areal bone mineral density of total hip, lumbar spine (L1-L4), femoral neck • Feasibility = Retention and adherence • Safety = adverse events related to exercise • Follow-up = 6 mths, 12 mths
Cormie et al (2015)[150]	Australia	• Local and metastatic PCa treated with ADT • n° tot = 63 IG = 32; CG = 31 • Mean age (year) = 68.3* (range: 46-80) • Time on ADT, Mean (SD) IG = 6.2 dys (1.6) CG = 5.6 dys (2.0)	• Bone metastasis • Previously treatment with ADT	IG = Supervised exercise PROGRAM involving aerobic and resistance exercise sessions CG = Standard care	• BMD = areal bone mineral density of whole body, lumbar spine (L2-L4), femoral neck • Follow-up = 3 mths
Newton et al (2019)[151]	Australia	• Local and metastatic PCa treated with ADT • n° tot = 154 IG = 57 (ImpRes), 50 (AerRe); CG = 47 • Mean age (year) = 69.0 ± 9.0 (SD) (range: 43-90) • Time on ADT, Mean (IQR) IG (ImpRe)= 3.0 mths (2.0-4.0); IG (AerRe)= 3.0 mths (2.0-4.0) CG = 2.0 mths (2.0-3.5)	• Bone metastasis	IG (ImpRe)= Supervised and unsupervised impact-loading and resistance exercise IG (AerRe) = Supervised aerobic and resistance exercise CG = Standard care	• BMD = whole body, total hip, lumbar spine (L2-L4), femoral neck, trochanter • Follow-up = 6 mths
Taaffe et al (2019)[152]	Australia	• Local PCa treated with ADT • n° tot = 104 IG = 54; CG = 50 • Mean age (year) = 68.2* (range: 48-84) • Time on ADT, Mean (SD) IG = 6.4 dys (2.1) CG = 5.7 dys (1.9)	• Osteoporosis • Previously treatment with ADT	IG = Supervised resistance+aerobic+impact exercise sessions CG = Standard care	• BMD = whole body, total hip, lumbar spine, • Follow-up = 6 mths
Nilsen et al (2015)[153]	Norway	• Local and metastatic PCa treated with ADT • n° tot = 58 IG = 28; CG = 30 • Mean age (year) = 66.0 (range: 54-76) • Time on ADT, Mean (SD) IG = 9.0 mths (1.6) CG = 9.0 mths (1.8)	• Osteoporosis	IG = Supervised and unsupervised of high-load strength PROGRAM CG = Standard care	• BMD = areal bone mineral density of whole body, total hip, total lumbar spine, femoral neck, trochanter • Feasibility = adherence • Follow-up = 4 mths
Uth et al (2016)[154]	Denmark	• Local and metastatic PCa treated with ADT • n° tot = 57 IG = 29; CG = 28 • Mean age (year) = 67.0 • Time on ADT, Mean (IQR) IG = 12.5 mths (9.5-27.8) CG = 18.7 mths (9.4-35.0)	• Osteoporosis	IG = Football training CG = Standard care	• BMD = areal bone mineral density of whole body, total hip, total lumbar spine, femoral neck, trochanter • Feasibility = adherence • Safety = adverse events • Follow-up = 3 mths
Uth et al					• BMD = areal bone mineral density

(2016)[155]					of whole body, total hip, total lumbar spine, femoral neck, trochanter • Feasibility = adherence • Safety = adverse events • Follow-up = 8 mths
Winters-Stone et al (2014)[175]	USA	• Local and metastatic PCa treated with ADT • n° tot = 51 IG = 29; CG = 22 • Mean age (year) = 70.2 • Time on ADT, Mean (SD) IG = 39.0 mths (36.1) CG = 28.5 mths (29.2)	• Bone metastasis • Osteoporosis	IG = Supervised impact and resistance training CG = Stretching exercise	• BMD = total hip, lumbar spine (L1-L4), femoral neck, greater trochanter • Follow-up = 6 mths, 12 mths
Kim et al (2018)[176]	South Korea	• Local and metastatic PCa treated with ADT • n° tot = 51 IG = 26; CG = 25 • Mean age (year) = 70.8 (range: 20-80) • Time on ADT, Mean (SD) IG = 22.5 mths (26.5) CG = 21.6 mths (19.1)	• Bone metastasis • Osteoporosis	IG = Unsupervised weight-bearing and resistance exercise with optional PROGRAM (stabilization/balance exercise + circuit resistive calisthenics) CG = Stretching exercise	• BMD = total hip, lumbar spine (L1-L4), femoral neck • Feasibility = Retention and adherence • Safety = adverse events related to exercise • Follow-up = 6 months
Lam et al (2020)[208]	Australia	• Local and metastatic PCa treated with ADT • n° = 25 IG = 13; CG = 12 Mean age (year) = 70.5* • Time on ADT IG: 0 dys CG: 0 dys	• Previous treatment with ADT (within the last 12 months)	IG = Home-based Progressive Resistance Training PROGRAM CG = Standard care	• BMD = Femoral neck and lumbar spine • Feasibility = Retention and adherence • Safety = adverse events related to exercise • Follow-up = 6 weeks, 6 months, 12 months

Abbreviations: PCa, prostate cancer; ADT, androgen deprivation therapy; IQR, interquartile range; IG, intervention group; CG, control group; SD, standard deviation; dys, days; BMD, bone mineral density; mths, months; ImpRe, impact+resistance training; AerRe, aerobic+resistance training.
*Estimated mean age of participants.

Feasibility outcomes: recruitment, retention, and adherence rates

The data of recruitment, retention, and adherence rates are reported in Table 3.3.

The recruitment rate for the RCTs included in this review ranged from 10.9%[175] to 73.1% [154,155]. The recruitment period ranged from 12 months [154,155] to 43 months [105].

Recruitment encompassed various modalities, including clinician referral [105,150–152,208], the screening of inpatients and outpatients of oncology and urology units [153–155,176], or combined strategies that also included enrolment from cancer registries, advertisements, and group/community events [105,175]. Most studies enrolled fewer patients than the number planned; only two studies were able to recruit the expected sample size [150,208].

Overall, the retention rate varied from 71.9% [155] to 100% [208]. Most studies (n = 8) reported a retention rate of > 80%, which had also been recorded at the 12-month follow-ups [105,175,208]. All but two studies [153,208] showed a higher retention rate in the intervention group (IG) than in the control group (CG). Overall, 55 men withdrew from the PE intervention, representing 15.6% of the 352 participants enrolled to the IG. Only six men dropped out due to reasons likely related to the intervention: four reported exercise-associated pain or muscle strain [153,154], one disliked the type of exercise proposed (football) [154], and another disliked the setting of exercise (clinic) [152]. Moreover, seven individuals dropped out due to low motivation to exercise [151,152]. However, most of the dropouts were among the participants allocated to CG (n = 66; 23.5%). All reasons for dropping out are reported in Table 3.4.

Adherence rates ranged from 43% [175] to 96.3% [150] in the IG and from 40% [176] to 74% [175] in the CG.

When PE interventions were supervised [105,150–155,175], the highest adherence rate was registered for the 3-month aerobic and resistance PE program (96.3%) [150], while the lowest was registered for the 8-month football training program (46.2%) [155]. Among the RCTs that experimented unsupervised PE [105,151,153,175,176,208], high adherence was shown when PE consisted of weight-bearing activities such as walking (84%) [176], and lower adherence was related to resistance plus impact exercises (49% and 43%) [105,175]. Two studies did not report data of adherence to unsupervised PE [151,153]. Two study designs implemented a stretching intervention for men allocated to CG. The adherence rate to this active control was equal to 74% when supervised and between 40% and 51% when unsupervised [175,176]. Printed exercise booklets [151] and 10-minute telephone sessions [176] were strategies used by some studies to facilitate adherence in the CG.

Table 3.3 Feasibility outcomes: recruitment, retention and adherence rates.

Study	Recruitment	Retention	Dropouts	Adherence
Dalla Via et al. (2021)[105]	• April 2014 - November 2017 • Recruited: 32.7% • Recruitment strategy: clinician referral, advertisements, and support group	• Study (6 mths): 91.4%* IG: 97.1%* CG: 86.1%*	• Study: n = 6 IG: n = 1 CG: n = 5	• IG: 65% (SE); 49% (UE)
		• Study (12 mths): 86.0% IG: 91.2%* CG: 80.6%*	• Study: n = 4 IG: n = 2 CG: n = 2	
Cormie et al. (2015)[150]	• June 2011 - October 2012 • Recruited: 50.0% • Recruitment strategy: clinician referral	• Study: 87.3%* IG: : 96.9%* CG: 77.4%*	• Study: n = 8 IG: n = 1 CG: n = 7	• IG: 96.3%
Newton et al. (2019)[151]	• 2009 – 2012 • Recruited: 58.1% • Recruitment strategy: clinician referral	• Study: 76.6%* IG: 73.7* (ImpRes); 86.0%* (AerRes) CG: 70.2%*	• Study: n = 36 IG: n = 15 (ImpRes); n = 7 (AerRes) CG: n = 14	• IG: 65% (ImpRes); 70% (AerRes)
Taaffe et al. (2019)[152]	• August 2013 – April 2015 • Recruited: 47.5% • Recruitment strategy: clinician referral	• Study: 81.7%* IG: 88.9%* CG: 74.0%*	• Study: n = 19 IG: n = 6 CG: n = 13	• IG: 79%
Nilsen et al. (2015)[153]	• December 2008 – December 2011 • Recruited: 14.0% • Recruitment strategy: screening of oncology and urology units	• Study: 84.5%* IG: 78.6%* CG: 90.0%*	• Study: n = 9 IG: n = 6 CG: n = 3	• IG: 88% (LB); 84% (UB)
Uth et al. (2016)[154]	• February 2012 – September 2013 • Recruited: 73.1% • Recruitment strategy: screening of outpatients of Urology units	• Study (3 mths): 86.0%* IG: 89.7%* CG: 82.1%*	• Study: n = 8 IG: n = 3 CG: n = 5	• IG: 76.5%
Uth et al. (2016)[155]		• Study (8 mths): 71.9%* IG: 72.4%* CG: 71.4%*	• Study: n = 8 IG: n = 5 CG: n = 3	• IG: 46.2%
Winters-Stone et al. (2014)[175]	• Over two years • Recruited: 10.9% • Recruitment strategy: clinician referral, enrolment from cancer registries, advertisements, support group and community events	• Study: 84.0% IG: 90.0% • CG: 77.0%	• Study: n = 8 IG: n = 3 • CG: n = 5	• IG: 84% (SE); 43% (HE) • CG: 74% (SE); 51% (HE)
Kim et al. (2018)[176]	• May 2013 - September 2015 • Recruited: 14.0% • Recruitment strategy: screening of outpatients of Urology units	• Study: 80.4%* IG: 88.5%* CG: 72.0%*	• Study: n = 10 IG: n = 3 CG: n = 7	• IG: 64.8% (RE); 84.7% (WBE) CG: 40%
Lam et al. (2020)[208]	• Over two years • Recruited: 62.5% • Recruitment strategy: clinician referral	• Study (6 weeks): 100.0%* IG: 100.0%* CG: 100.0%*	• Study: n = 0 IG: n = 0 CG: n = 0	• IG: 100%
		• Study (6 mths): 92.0%* IG: 92.3%* CG: 100.0%*	• Study: n = 1 IG: n = 1 CG: n = 0	• IG: 82.5%
		• Study (12 mths): 80.0%* IG: 76.9%* CG: 83.3%*	• Study: n = 4 IG: n = 2 CG: n = 2	• IG: 77.9%

Abbreviations: IG, intervention group; CG, control group, ADT, androgen deprivation therapy; ImpRes, impact+resistance exercise, AerRes, aerobic+resistance exercise; RE, resistance exercise; WBE, weight bearing exercise; LB, lower body; UB, upper body; RT, radiation therapy; SE, supervised exercise; HE, home-based exercise; UE, unsupervised exercise.

*Calculated from the CONSORT diagram of the study.

Table 3.4 Reasons of dropping out.

Reason	Intervention Group (n)	Control Group (n)
Become ineligible	4	6
Health issues	27	19
Lost to follow-up	1	6
No longer interested in	7	10
Personal issues	5	7
Time constraints	3	4
Too far to travel	--	2
Want to exercise at home	1	--
Wanted to start exercising	--	8
Death	3	2
Other	4	2

Safety outcome

The safety of interventions is summarized in Table 3.4. Although all the studies included in this review monitored the AEs associated with experimental PE, only three studies described how AEs were recorded [105,154,155,176], and two reported how their severity was defined [154,155,176]. Uth et al.[154,155] complied with existing guidelines [209], and Kim et al. [176] recorded falls, injuries, and exercise-associated symptoms as AEs attributable to PE. Overall, 30 AEs were related to PE [105,153–155,208] three were classified as severe (two fibula fractures and one partial Achilles tendon rupture) [154] and 27 were minor musculoskeletal AEs [105,153,154,208]. In the other studies, no AEs were reported.

In one study, the PE intervention was adapted to meet the needs of two men who had knee and shoulder discomfort due to the high workload [175]. However, a large number of AEs not attributable to PE were reported as generic health issues/hospitalization (n = 13 IG, n = 17 CG) [105,151–153,155,175,176,208], injury/accident (n = 8 IG, n = 2 CG) [151–153], and death (n = 3 IG, n = 2 CG) [105,151,175]. In a few cases, AEs were reported as pain (n = 1 CG) [153], fatigue (n = 1 CG) [152], ADT side effects (n = 1 IG) [150], and peripheral neuropathy (n = 1 IG) [154,155].

Characteristics of experimental PE: components, posology, and setting

Table 3.5 reports the main features of the PE programs. The duration of PE varied from three [150,154] to twelve months [105,175,208]. Most studies implemented a multicomponent experimental PE consisting of aerobic exercise associated with resistance exercise [150,151,176] or with impact-loading exercise [152], or consisting of resistance exercise and impact-loading exercise [105,151,175]. Two studies implemented a single-component resistance training program [153,208], and another included balance and core stability exercises [105].

Resistance training consisted of exercises targeting the major upper and lower body muscle groups and involving free weight, weight machines, or resistance bands [105,150–153,175,176,208]. Six studies reported that training intensity was progressively increased at 2–5% [153,175,176] or 5-10% increments [150–152], with reference to the individual target defined through a repetition maximum test [151–153,175].

Impact exercise consisted of drop jumping activities either alone [175] or combined with a series of bounding, hopping, skipping, and/or leaping [105,151,152]. The intensity of these activities was set as the percentage of body weight and was progressively increased over time [105,151,152,175].

Aerobic exercise consisted of weight bearing activities such as walking or jogging [150–152,176], cycling or rowing on a stationary ergometry [105,150–152], or exercising on a cross trainer machine [150,151]. Aerobic activities were performed for from 15 to 40 minutes, one to two times/week at the intensity of 55% to 85% of the maximum heart rate [105,150–152] or with the aim of reaching 150 min/week of moderate-intensity exercise [176]. Exercise intensity during sessions was frequently monitored by way of a perceived exertion scale, asking individuals to exercise at a level between “somewhat hard” to “hard” [150,152,176].

It should be noted that one study implemented football training, which can be considered a combination of aerobic, resistance, and impact exercise [154,155]. The intensity of football training was progressively increased both in the number and in the duration of sessions for the first three months [154], then a maintenance program was undertaken for the following five months [155].

In most cases, the PE session lasted 40 to 60 minutes and was performed two to three times/week [105,150,152–155,175,208], and even four to five times/week [151,176].

Frequently, PE sessions began with warm-up and ended with cool down exercises or relaxation activities [105,150–152,154,155,176].

The PE sessions were either completely supervised [150–152,154,155], unsupervised [176,208], or a mix of supervised and unsupervised [105,151,153,175]. Supervised sessions were administered to groups [105,150–155,175] and performed in exercise clinics [150–153,175] or a gym [105], or in sport settings (natural grass pitch or indoors for football training) [154,155]. Unsupervised sessions could be implemented individually [151,155,175,208] or in groups [153] and were performed at home [105,151,175,176,208], at a gym [105], or in exercise clinics [153].

In most studies, the men allocated to the CG were encouraged to engage in exercise or to maintain their habitual physical activity level, while two studies implemented a full body stretching program for individuals allocated to CG [175,176].

Supplementary interventions

Several study designs also implemented a supplementary home-based program for men allocated to IG, with a frequency of two to five times/week: two studies proposed aerobic exercise to accumulate 150 min/week [150,151]; one proposed a combination of aerobic with impact exercise [152]; one study proposed a stabilization/balance exercise and circuit resistive calisthenics [176].

Some studies also provided the men allocated to experimental PE with educational counseling or educational material regarding exercise [176,208], exercise logs where the men recorded the PE activities performed individually [151,152,176,208], or monthly reminder phone calls [208]. Moreover, one study experimented PE associated with daily multi-nutrient supplementation compared to vitamin D only for the control group [105], and another study provided calcium and vitamin D supplementation for both the intervention and the control groups [152].

Table 3.5 Details of PE programs and safety outcomes.

Study	Detailed intervention IG	Detailed Intervention CG	Adverse events
Della Via et al. (2021)[105]	● Intervention period: 12 mths ● Supervised exercise in health and fitness facility (gym) - Aerobic exercise: 55-75% max HR x 15-25 min; - Resistance exercise: 3-8 RPE, 2 sets x 8-15 reps - Weight-bearing, impact exercise: 1-9 times BW, 3 sets x 10-20 reps - Balance/functional exercise: 2 sets of 30-60 sec or for given number of reps - Core stability exercise: 2 sets x 10-15 reps Modality: N.R. Each session: ~ 60 min (with warm-up and cooldown), 2 d/w (after 6 mths only one session was supervised) ● Unsupervised exercise in home-setting - Similar at supervised one but used BW and resistance bands Modality: individual Each session: 20-60 min, 1 d/w	● No intervention	● Referred to exercise: IG: 21; CG: 0* ● Not referred: IG: 3; CG:5
Cormie et al. (2015)[150]	● Intervention period: 3 mths ● Supervised exercise in exercise clinic - Aerobic exercise: 70-85% max HR x 20-30 min; - Resistance exercise: 6-12 RM x 1-4 sets Modality: group Each session: ~ 60 min (with warm-up and cooldown), 2 d/w ● Supplemental exercise: home-based aerobic activity in order to accumulate 150 min/wk	● No intervention	● Referred to exercise: IG: 0; CG: 0 ● Not referred: IG: 1; CG:0
Newton et al. (2019)[151]	ImpRes ● Intervention period: 6 mths ● Supervised exercise in exercise clinic - Resistance exercise: 6-12 RM x 2-4 sets - Impact exercise: 3-5 times BW x 2-4 sets Modality: group Each session: 60 min (with warm-up and cooldown), 2 d/w ● Unsupervised exercise in home-setting - Impact exercise: 2-4 sets Modality: individual Each session: 2 d/w AerRes ● Intervention period: 6 mths ● Supervised exercise in exercise clinic - Resistance exercise: 6-12 RM x 2-4 sets - Aerobic exercise: 60-85% max HR x 20-30 min Modality: group Each session: 60 min (with warm-up and cooldown), 2 d/w ● Supplemental exercise: home-based aerobic activity in order to accumulate 150 min/wk	● Printed booklet with information about exercise	● Referred to exercise: IG: 0 (ImpRes), 0 (AerRes); CG: 0 ● Not referred: IG: 8 (ImpRes), 2 (AerRes); CG: 4
Taaffe et al. (2019)[152]	● Intervention period: 6 mths ● Supervised exercise in exercise clinic	● No formal intervention	● Referred to exercise: IG: 0; CG: 0

	- Aerobic exercise: 60-85% max HR x 25-40 min - Resistance exercise: 6-12 RM x 2-4 sets - Impact exercise: 3.4-5.2 times BW x 2-4 sets Modality: group Each session: ~ 60 min (with warm-up and cooldown), 3 d/w (Aerobic and resistance exercise were performed in alternated session days) ● Supplemental exercise: home-based aerobic activity + modified impact-loading exercise x 2 d/wk		● Not referred: IG: 3; CG: 7
Nilsen et al. (2015)[153]	● Intervention period: 4 mths ● Supervised exercise in clinic exercise - Resistance exercise: 6-10 RM x 1-3 sets Modality: group Each session: 2 d/w ● Unsupervised exercise in clinic exercise - Resistance exercise: 80-90% of 10 RM x 2-3 sets x10 rep Modality: group or individual Each session: mid-week session (1 d/w)	● Encouraged to maintain their habitual physical activity level	● Referred to exercise: IG: 3; CG: 0 ● Not referred: IG: 3; CG: 3
Uth et al. (2016)[154]	● Intervention period: 3 mths ● Supervised exercise on pitch (out/indoors) - Football exercise: 2-3 sets x 15 min Modality: group Each session: 45-60 min (with warm-up), 2-3 d/wk	● Encouraged to maintain their habitual physical activity level	● Referred to exercise: IG: 5; CG: 0* ● Not referred: IG: 4; CG: 0
Uth et al. (2016)[155]	● Intervention period: 8 mths ● Supervised exercise on pitch (out/indoors) - Football exercise: 3 sets x 15 min Modality: group Each session: 60 min (with warm-up), 2 d/wk		
Winters-Stone et al. (2014)[175]	● Intervention period: 12 mths ● Supervised exercise in exercise clinic - Resistance exercise Upper body: 8-15 RM x 1-2 sets x 8-14 reps Lower body: 0-15% BW x 1-2 sets x 8-12 reps - Impact exercise: 0-10% BW x 1-10 sets x 10 reps Modality: in group Each session: 60 min, 2 d/wk ● Unsupervised exercise in home-setting - Similar at supervised one with resistance bands that replaced weighted vest used in impact exercise Modality: individual Each session: 60 min, 1 d/wk	● Intervention period: 12 mths ● Supervised exercise in exercise clinic - Whole body stretching and relaxation exercise in a seated or lying position Modality: in group Each session: 60 min, 2 d/wk ● Unsupervised exercise in home setting - Similar at supervised one Modality: individual Each session: 60 min, 1 d/wk	● Referred to exercise: IG: 0; CG: 0 ● Not referred: IG: 1; CG: 3
Kim et al. (2018)[176]	● Intervention period: 6 mths ● Unsupervised exercise in home-setting - Resistance exercise: 0-10% BW x 2-3 sets x 8-15 reps; - Weight-bearing exercise: 11-15 RPE x 20-30 min Modality: individual Each session: started with a warm-up, 2-5 d/w of resistance exercise; 3-5 d/w of weight-bearing exercise ● Optional program: stabilization/balance exercise + Circuit resistive calisthenics x 2-5 d/wk	● Intervention period: 6 mths ● Unsupervised Stretching in home setting - Whole body stretching (lying, sitting, standing) Modality: individual Each session: 20 min, 3-5 d/wk	● Referred to exercise: IG: 0; CG: 0 ● Not referred: IG: 1; CG:0

Lam et al. (2020)[208]	● Intervention period: 12 mths ● Unsupervised exercise in home-setting - Resistance exercise: 8-12 RM x 3 sets Modality: individual Each session: 40 min, 3 d/w	● No intervention	● Referred to exercise: IG: 1; CG: 0 ● Not referred: IG: 0; CG:1

Abbreviations: IG, intervention group; CG, control group; HR, heart rate; RM, repetition maximum; d/wk, days per week; min/wk, minutes per week; BW, body weight; RPE, rate of perceived exertion; Reps, repetitions; ImpRes, impact+resistance exercise; AerRes, aerobic+resistance exercise.
*Adverse events were not monitored in the CG.

DISCUSSION

This systematic review suggests that PE is feasible and safe in men with PCa undergoing ADT. Recruitment and adherence rates varied between studies, but the latter was frequently higher in the experimental intervention group than in the control group. Most studies reported a retention rate of > 80% [105,150,152–154,175,176,208], with higher rates registered for the intervention groups [105,150,151,154,155,175,176]. Finally, thirty AEs were associated with experimental PE [105,153–155,208]: three were classified as severe, and all were associated with football training [154,155].

It is well known that participation in trials of cancer survivors is a challenge, especially for populations over age 65 [210,211]. The average age of the study samples included in this review was between 66–71.0 years, with five of the included studies that reached a recruitment rate of close to 50% or over (47.5%-73.1%) [150–152,154,155,208]. Moreover, seven studies reached 80% of the sample size set a priori [150–153,175,176,208]. The retention rate was quite high in all the studies included. The adherence rate for individuals allocated to IG ranged from 43% [175] to 96.3% [150], suggesting that PE is feasible in this population.

The feasibility of the experimental PE may have been influenced by several factors, for example, the recruitment strategy applied. The most successful recruitment strategy seemed to be clinician referral [150–152,208], while advertisements and community events did not seem to add any substantial advantage [105,175].

The retention rate was > 70% in all the included studies; few individuals (6 out of 51) dropped out due to reasons attributable to the experimental PE, although dropouts were more frequent in the CG. This might suggest that exercise is well tolerated and appreciated in this population, even if men with PCa undergoing ADT are often older, fragile individuals with health issues that might influence participation in exercise. A frequently reported reason for dropping out was the loss of interest in the study: this finding supports the importance of adequate strategies to sustain participants' interest during the trial (e.g., follow-up phone calls, adequate progression of intensity of exercise) [212], including the proposal of an active control (such as stretching or alternative exercise) to avoid patients' dropping out due to their desire to start exercising.

Furthermore, this review shows a higher adherence rate to supervised (range: 46% - 96%) rather than to unsupervised PE (range: 40% - 84%), confirming the value of having a supervisor during the training sessions in this population [213,214]. However, two studies [176,208], which proposed completely unsupervised PE supported by education material and monitoring of exercise by phone, reported an adherence rate of > 60%.

Concerning the safety of exercise, thirty AEs were associated with football training, resistance exercise, and resistance plus impact exercise [105,153–155,208]; of these AEs, three were severe, all occurring during football training [154,155]. Nevertheless, most studies did not record AEs or they did not comprehensively report AE monitoring and the recording procedures followed [150–152,176,208]. Of note, many AEs arose from health issues not associated with exercise. Thus, we suggest a well-defined definition and recording of any AEs in future similar studies to accurately evaluate the safety of interventions that require the long-term commitment of fragile individuals. Regarding this issue, while current guidelines and standard protocols have been developed to help researchers in all biomedical fields to systematically report AEs of experimental interventions [198,215], a specific guideline for reporting AEs associated with physical activity interventions in physical therapy studies would address this important issue.

Moreover, in the studies included in this review, the intensity of the experimental PE was moderate to high, in accordance with guidelines for exercise in older adults [142]. Nevertheless, the intensity of the training session in most studies was personalized to the individuals' capabilities in order to ensure safety and compliance [105,150,151,153,175,176,208].

Limitations

This systematic review has some limitations. First, the lack of standardized procedures to measure adherence and AEs may have biased the feasibility and safety estimates of PE in this population.

With respect to adherence, all the studies included provided a mean cumulative rate, regardless of the type of exercise proposed. Thus, the estimate of patients' adherence to the prescribed PE program should be interpreted with caution, given the lack of information concerning the components of PE being experimented. With respect to AEs, several studies did not report the monitoring procedures for AEs adopted, nor the type or number of AEs that occurred. Thus, an overestimate of safety cannot be ruled out.

Moreover, data regarding time from diagnosis, cancer stage, ADT treatment duration, and concurrent cancer treatments of individuals who participated in the original studies were not thoroughly reported, thus hindering the generalizability of the results of this review.

CONCLUSIONS

Multicomponent PE implemented according to guidelines for exercise in older men with PCa undergoing ADT [57] seems feasible. Future research should undertake well-designed clinical trials to assess the effectiveness of high-intensity PE programs that include structured neuromotor exercises, such as balance, agility, coordination, and cognitive exercises [57,142]. Researchers should include standardized methods to record AEs, especially when high-impact exercises (e.g., football training) are applied. Moreover, outcome measures should go beyond the measurements of BMD, focusing on the impact of PE on clinically relevant endpoints such as the risk of accidental falls and fractures.

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Conflict of interest/competing interest

None declared.

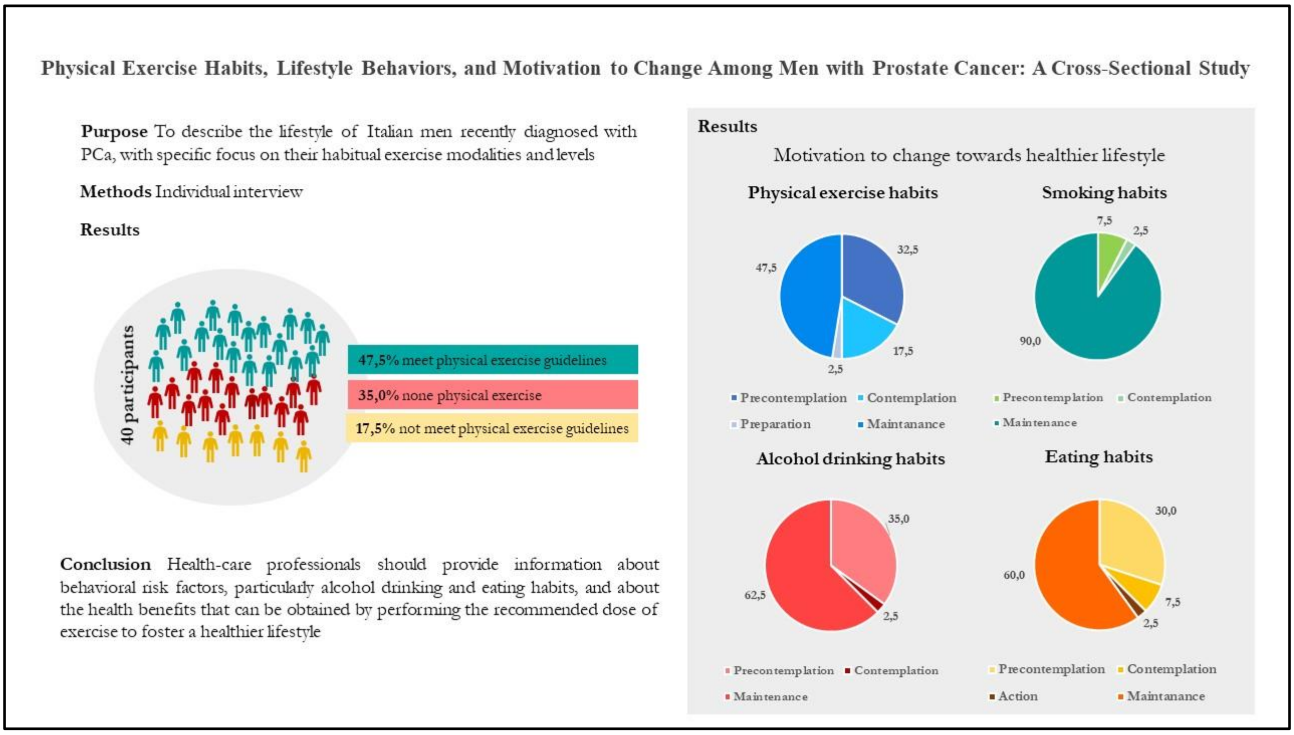
Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

CHAPTER IV

Observational study

Physical exercise habits, lifestyle behaviors and motivation to change among men with prostate cancer: a cross sectional study[c]



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Barbara Bressi[1,2], Maribel Cagliari[3], Cinzia Iotti[4], Stefania Fugazzaro[2], Silvio Cavuto[5], Franco Antonio Mario Bergamaschi[6], Alfredo Moscato[6] & Stefania Costi[3,7].

Affiliations:

[1]PhD Program in Clinical and Experimental Medicine, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Reggio Emilia, Italy.
[2]Physical Medicine and Rehabilitation Unit, Azienda USL–IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[3]Department of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy.
[4]Department of Oncology and Advanced Technologies, Radiotherapy Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[5]Research and Statistics Infrastructure, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[6]Urology and Mininvasive Surgery, Department of General and Specialist Surgeries, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[7]Scientific Directorate, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.

ABSTRACT

Purpose: To describe the physical exercise (PE) habits, lifestyle, and the motivation to change towards healthier behaviors in patients newly diagnosed with prostate cancer (PCa).

Methods: A cross-sectional study was conducted in an Italian hospital setting. Men newly diagnosed with PCa were consecutively invited to participate in a structured interview that was conducted either in person or by telephone.

Results: The mean age of the 40 participants was 70.5 ± 6.6 (mean ± SD, range 50-84). Most participants (65%) reported they were physically active, but more than half of the sample did not reach the recommended PE level. However, 40% of participants were interested in participating in an exercise program. Only 10% of participants were current smokers, but 90% drank alcohol, and 62.5% were overweight/obese. Almost all participants were not willing to change their habits.

Conclusions: A high proportion of men interviewed are insufficiently active when diagnosed with PCa. Moreover, even when exposed to behavioral risk factors, they are not willing to change their lifestyle. Health-care professionals who deal with men newly diagnosed with PCa should take advantage of the teachable moment and apply strategies that support patients' motivation to exercise and adherence to healthier lifestyles.

Trial registration: The study was prospectively registered in ClinicalTrial.gov NCT03982095 on June 11, 2019.

Keywords: prostatic neoplasms; exercise; lifestyle; guideline adherence; health behavior; trans-theoretical model.

INTRODUCTION

Prostate cancer (PCa) ranks second in global cancer incidence [3], with 1.414.259 new cases diagnosed worldwide in 2020, and its incidence increases with age [2].

PCa impacts on quality of life due to the numerous side effects of treatments [5]. Physical exercise (PE) has been suggested as a strategy to improve the quality of life of patients with PCa [10], as it supports the improvement of psychological well-being, incontinence, physical performance, fatigue, body composition, bone health, and muscle strength [145,194,214,216]. Guidelines for exercise in cancer survivors recommend moderate-intensity aerobic exercise be performed a minimum of 30 minutes three times per week [81]. Moreover, resistance exercise performed twice per week at the appropriate intensity, i.e., two sets of 8-15 repetitions at 60% of maximum exertion for large group muscles, is recommended [81,86]. As PE should be performed regularly [88], behavior change is considered essential within any complex intervention targeting patients with cancer [217,218]. Initial evidence suggests that a healthy lifestyle, including regular PE, a balanced diet, weight control, and little or no exposure to risk factors such as alcohol and smoking can prevent the risk of cancer and can counteract the side effects of cancer treatments [79,80]. Despite PE having received widespread endorsement from several international institutes [80,81,86], only 13% of patients with PCa exercise regularly and meet the recommended levels of PE [219].

Evidence suggests that PE adherence can improve among patients with PCa if individualized support is provided [220]. Accordingly, strategies to improve the feasibility and acceptability of PE in this population have been described in the literature, indicating that supervision and group sessions act as facilitators [221,222]. Nevertheless, encouraging people to participate in regular exercise is difficult, especially for sedentary and older patients with cancer, who are usually underrepresented in exercise-based intervention studies [195,223]. Previous studies supported the use of the transtheoretical model (TTM) [224] to determine both individuals' habitual exercise behavior and their intentional behavior change with respect to regular exercise [225,226]. This knowledge may help health-care professionals to implement strategies that are tailored to the individual and effective in supporting adherence to PE. Acting on individual motivation, this model can support patients with PCa to achieve the recommended PE level during their lifespan.

To date, several studies have investigated the effectiveness and the feasibility of complex interventions that promote regular exercise and healthy lifestyle in patients with PCa [227,228]. However, to our knowledge, no study has analyzed the lifestyle of patients with newly diagnosed PCa and their motivation to change toward healthier habits.

Therefore, this cross-sectional study aimed to describe the lifestyle of Italian men recently diagnosed with PCa, focusing on their preferred exercise modalities and habitual PE levels. We also investigated the barriers and motivation to change towards healthier habits in this population.

METHODS

Participants and recruitment

This cross-sectional study was approved by the Local Ethics Committee of the Azienda USL-IRCCS di Reggio Emilia, Italy (June 06, 2019, number 425/2019/OSS/AUSLRE). A convenience sampling method was used to recruit patients between September 2019 and August 2021. Recruitment was conducted at the Urology and the Radiotherapy Units of the Santa Maria Nuova Hospital of Reggio Emilia. The referring physicians provided adult males (≥ 18 years) newly diagnosed PCa with brief written informational leaflet concerning the study. Patients who agreed to be contacted by a research staff member then received complete information and subsequently participated in the study if they were willing and if able to speak Italian. Exclusion criteria were recent major surgery or severe illness which caused a change in lifestyle in the three months prior to PCa diagnosis.

The strengthening the reporting of observational studies in epidemiology (STROBE) guidelines for cross-sectional studies were followed in the reporting of this study [229].

The study was prospectively registered in ClinicalTrial.gov NCT03982095.

Interview procedures

Each participant provided informed consent before the interview, which was conducted either in person or by telephone. The interview was structured and included 40 closed- and open-ended questions on these main themes:

- habitual PE levels, preferences, barriers and facilitators to exercise
- smoking, alcohol drinking, and eating habits
- motivation to change towards a healthier lifestyle.

On average, the interviews lasted 40 minutes. They were conducted and transcribed verbatim by the researcher who conducted the interview. Although the interview was structured, the interviewer could deviate from the open-ended questions to encourage a more in-depth conversation regarding each patient's lifestyle and his desire for change. For this purpose, open-ended questions were based on Prochaska and Di Clemente's Transtheoretical Model of Change [224] to classify participants on the basis of their motivation to change toward a healthier lifestyle.

According to this model, individuals move through five stages as they adopt and maintain new behaviors, which contribute to a patient's progression along the continuum of change [224]. The first stage is precontemplation, when there is no intention to change the behavior. The second is contemplation, when there is serious consideration about changing the behavior, followed by preparation, which shows commitment to behavior change in the near term. The fourth stage is action, when the behavior is successfully modified. The fifth and final stage is maintenance, which begins when the new behavior has been sustained for 6 months and has become part of the individual's lifestyle [224]. The model also includes the construct of decisional balance (i.e., weighing the pros and cons of the change) and self-efficacy (i.e., confidence in one's ability to engage in the specific healthy behavior), which contribute to a patients' progression along the continuum of change, through the TTM stages [226]. The interview is available in Supplementary material Table S4.1.

Measures and data analysis

First, data collected were analyzed through a descriptive statistic. Mean and standard deviation (SD) were used to summarize continuous variables, whereas counts and frequencies were used to summarize categorical variables. The answers to open-ended questions were categorized based on the themes that emerged (this means grouped by similar themes). The results are presented as a frequency distribution of answers for each category indicated. We collected the participants' sociodemographic characteristics and clinical and anthropometric data, including age, residence, marital status, education level, employment status, PCa staging, current/scheduled PCa treatments and any other current therapies, health status, and cognitive status. The Mini-Mental State Examination (MMSE) and its Italian telephone version (Itel-MMSE) were used to investigate cognitive impairment [230–232], while the Charlson Comorbidity Index (CCI) measured the presence of comorbidities [233].

Self-reported weight and height were used to calculate body mass index (BMI), which was then classified into three categories: < 25 (normal), 25–30 (overweight), > 30 (obese). The participants' PE level was assessed according to one of two categories: a) not meet aerobic PE guidelines, which includes those who perform < 150 min of moderate aerobic physical activity weekly; b) meet aerobic PE guidelines, which includes those who perform ≥ 150 min of moderate aerobic physical activity or 75 min of vigorous aerobic physical activity weekly, or an equivalent combination, i.e., PE volume that meets guideline recommendations [86].

Questions investigating smoking, alcohol drinking, and eating habits were based on the indexes used by the Italian National Institute of Health for the Italian behavioral risk factors surveillance system (PASSI) [234], which is based on the United States CDC's Behavioral Risk Factor Surveillance System [235]. Individuals were categorized as smokers, non-smokers, and ex-smokers. Smokers included current smokers and individuals who had quit smoking no more than 6 months earlier. Non-smokers included not currently smokers who claimed to have smoked fewer than 100 cigarettes in their life. Ex-smokers included not currently smokers who had quit smoking more than 6 months earlier and who claimed to have smoked a minimum of 100 cigarettes in their life. Regarding alcohol drinking, individuals were categorized as high-risk drinkers (>2 alcohol units/day), moderate drinkers (≤2 alcohol units/day), and nondrinkers (no alcohol consumption at all). We have investigated the quantity, quality, and variety of food intake. Specifically, we investigated whether the patients habitually consumed snacks, sweets, and/ or prepackaged foods, whether they ate at regular times, and whether they paid attention to eating healthier (i.e., quality and/or variety and/or cooking methods) [234,235]. We categorized the patients' motivation to change their eating habits based on their satisfaction with their diet and their willingness to improve some of the above-mentioned aspects of their diet.

We also collected data on the participants' perceived health status, the perceived relevance of PE, and the perceived relevance of feeling fit and of adopting healthier habits. The relevance of PE and the relevance of adopting a healthy lifestyle were categorized into four levels: not at all important, not very important, quite important, very important.

RESULTS

Participants' Characteristics

Of the 77 patients who were eligible, 40 were interviewed (response rate of 51.9%). Figure 4.1 shows the flow diagram of participants. On average, participants were 70.5 ± 7.6 years old (range 50-84), with adequate cognitive status (average MMSE score 27.0 ± 1.2). More than half of the participants (55%) reported at least one chronic comorbidity, and 62.5% were overweight or obese. Most participants were married (80%), with a low (42.5%) or medium (37.5%) education level. At the time of the interview, 67.5% of men were retired, while 32.5% were still employed full-time (n = 11) or part-time (n = 2). See Table 4.1 for a summary of participants' sociodemographic and clinical data.

Figure 4.1 Flow diagram of study participants (STROBE statement [229]).

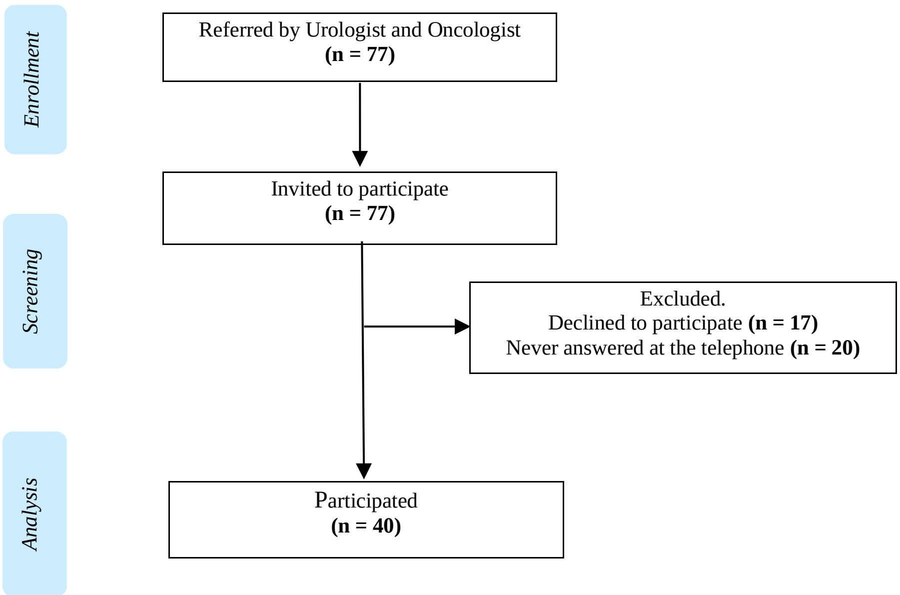


Table 4.1 Descriptive analysis of participants for adherence to the PE guidelines by sociodemographic and clinical characteristics.

		Total	Not meet aerobic PE guidelines	Meet aerobic PE guidelines
		N (%)	N (%)	N (%)
		40 (100.0)	21 (52.5)	19 (47.5)
Sociodemographic factors				
Age category	Aged (≥ 65)	32 (80.0)	16 (50.0)	16 (50.0)
	Middle-aged (45-64)	8 (20.0)	5 (62.5)	3 (37.5)
Education level[a]	Low	17 (42.5)	11 (64.7)	6 (35.3)
	Medium	15 (37.5)	7 (46.7)	8 (53.3)
	High	8 (20.0)	3 (37.5)	5 (62.5)
Marital status	Married/live together	32 (80.0)	18 (56.3)	14 (43.8)
	Divorced/Separated	4 (10.0)	2 (50.0)	2 (50.0)

	Unmarried	3 (7.5)	1 (33.3)	2 (66.7)
	Widower	1 (2.5)	0 (0.0)	1 (100.0)
Location	Rural	27 (67.5)	15 (55.6)	12 (44.4)
	Urban	13 (32.5)	6 (46.2)	7 (53.8)
Household composition	Lives with other cohabitant(s)	34 (85.0)	18 (52.9)	16 (47.1)
	Lives alone	6 (15.0)	3 (50.0)	3 (50.0)
Employment status	Retired	27 (67.5)	16 (59.3)	11 (40.7)
	Employed	13 (32.5)	5 (38.5)	8 (61.5)
Clinical characteristics				
BMI category[b]	Normal weight	15 (37.5)	7 (46.7)	8 (53.3)
	Overweight	16 (40.0)	7 (43.8)	9 (56.3)
	Obese	9 (22.5)	7 (77.8)	2 (22.2)
PCa staging	Stage I	25 (62.5)	14 (56.0)	11 (44.0)
	Stage II	8 (20.0)	5 (62.5)	3 (37.5)
	Stage III	4 (10.0)	2 (50.0)	2 (50.0)
	Stage IV	3 (7.5)	0 (0.0)	3 (100.0)
Current/scheduled treatment	Hormone therapy[c]	19 (47.5)	9 (47.4)	10 (52.6)
	Radiotherapy	30 (75.0)	16 (53.3)	14 (46.7)
	Radical prostatectomy	8 (20.0)	4 (50.0)	4 (50.0)
	None	1 (2.5)	0 (0.0)	1 (100.0)

Abbreviations: PE, physical exercise; BMI, body mass index;
[a]Low education level = primary school and middle school; Medium education level = high school, High education level = university or post-university degree. [b]BMI category = BMI < 25 normal weight; BMI ≥ 25 overweight; BMI ≥ 30 obese. [c]Not all percentages total 100 because hormone therapy is used alone or in association with other treatments.

PE Attitudes and Motivation to Change Towards PE

Despite the fact that most of the interviewees (65.0%) declared they were physically active, more than a half (52.5%) did not meet the current recommendations of PE levels, and 35% did not engage in any PE. Men participated in a range of exercise activities, such as walking or jogging (47.5%), strength and flexibility exercise activities performed at the gym or at home (20.0%), bicycling (17.5%), and other sports activities (12.5%), such as volleyball (n = 1), dancing (n = 1), skiing (n = 2), golf (n = 2) tennis (n = 1), and swimming (7.5%). Gardening was also frequent (20.0%), but only for men that did not meet the PE guidelines.

Almost all participants acknowledged the physical and psychological benefits of PE, but 32.5% believed that including regular PE among their habits would not be feasible due to a lack of time or interest (n = 13). Few participants thought that exercise would not be beneficial (n = 2), or that it would be inappropriate or unsafe given their general health conditions (n = 3). Further, 12.5% of participants who did not sufficiently engage in regular exercise thought that PE was not important.

The most frequently recognized benefits of PE on health were its psychological and physical benefits (65.0%), feeling fit/weight control (40.0%), and increased muscle strength (37.5%). Even though most participants stated that regular PE would be feasible and could be included among their habits (67.5%), only 40% stated they would like to participate in a long-term structured PE program with a supervised and an unsupervised period, that included aerobic, resistance, impact, and neuromotor exercises to improve their health. Conversely, 40% stated that they would definitely not participate and 20% were uncertain. Data are presented in Table 4.2.

Table 4.2 Descriptive analysis of participants PE level by PE attitudes and motivation to change PE habits.

		Total	Not meet aerobic PE guidelines	Meet aerobic PE guidelines
		N (%)	N (%)	N (%)
		40 (100.0)	21 (52.5)	19 (47.5)
PE attitudes				
Regular PE	Yes	26 (65.0)	7 (26.9)	19 (73.1)
	No	14 (35.0)	14 (100.0)	0 (0.0)
Type of PE[a]	Walking/jogging	19 (47.5)	4 (21.1)	15 (78.9)
	Exercise activities (at gym and/or home) [b]	8 (20.0)	1 (12.5)	7 (87.5)
	Stationary bike/bicycling	7 (17.5)	2 (28.6)	5 (71.4)
	Other sport activities[c]	5 (12.5)	0 (0.0)	5 (100.0)
	Swimming	3 (7.5)	1 (33.3)	2 (66.7)
	Gardening	8 (20.0)	8 (100.0)	0 (0.0)
Relevance of PE	Quite/very important	35 (87.5)	16 (45.7)	19 (100.0)
	Not/not very important	5 (12.5)	5 (100.0)	0 (0.0)
Motivation to change PE habits				
Feasibility of PE	Yes	27 (67.5)	12 (44.4)	15 (55.6)
	No	13 (32.5)	9 (69.2)	4 (30.8)
PE impact on own health[a]	Physical and psychological well-being	26 (65.0)	15 (57.7)	11 (42.3)
	Feeling fit/weight control	16 (40.0)	9 (56.3)	7 (43.8)
	Increase muscle strength	15 (37.5)	8 (53.3)	7 (46.7)
	Remain active (mental health)	9 (22.5)	5 (55.6)	4 (44.4)
	Relaxing	5 (12.5)	4 (80.0)	1 (20.0)
	Good mood/self-esteem	4 (10.0)	3 (75.0)	1 (25.0)
	Help to follow a healthy diet	4 (10.0)	0 (0.0)	4 (100.0)
	Not sure	3 (7.5)	1 (33.3)	2 (66.7)
	Not useful	2 (5.0)	1 (50.0)	1 (50.0)
Willing to participate in a structured long-term PE	No	17 (42.5)	13 (76.5)	4 (23.5)
	Yes	16 (40.0)	4 (25.0)	12 (75.0)
	Not sure	7 (17.5)	4 (57.1)	3 (42.9)

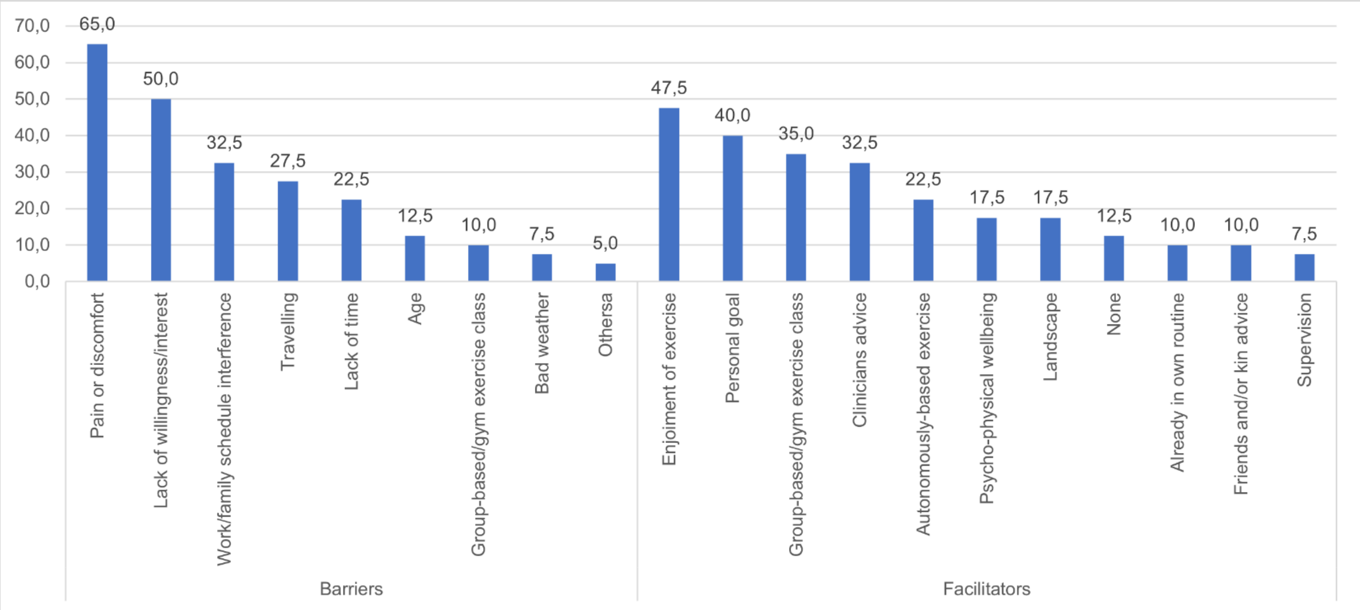
Abbreviations: PE, physical exercise.
[a]Multiple responses were possible.
[b]Exercise activities were carried out 2-3 times/week and included: resistance exercise (n = 8, at home = 6; at the gym = 2) with breathing exercises at home (n = 1), and/or stretching exercises (at home = 2, at the gym = 1).
[c]Other sports activities included volleyball (n = 1), dancing (n = 1), skiing (n = 2), golf (n = 2) and tennis (n = 1).

Perceived Barriers and Facilitators to PE

The most common barriers reported to engaging in regular PE were pain or discomfort (65%), lack of willingness/interest (50%), and interference with daily schedule such as work and family commitments (32.5%). The distance from a sports facility (e.g., gym, swimming pool, etc.) and a lack of time were also considered as barriers to exercise (27.5% and 22.5%, respectively). Finally, 12.5% of men reported their age as a barrier to PE.

Factors acting as facilitators were the pleasure/enjoyment associated with exercising (47.5%), the possibility of achieving health goals or improving performance (40%), and exercising in a group (30%). Further motivational factors included advice from one’s physician (22.5%), and the psychophysical well-being associated with exercise (17.5%). Participants also recognized that both autonomously-based exercise and supervision could facilitate their adherence (respectively 22.5% and 7.5%). The most common facilitators and barriers to PE are reported in Figure 4.2.

Figure 4.2 Perceived barriers and facilitators to PE in Italian men newly diagnosed with PCa (n = 40).



[a]Included autonomously-based exercise class (n. 1) and cost (n. 1).
Multiple responses were possible.

Smoking, Alcohol Drinking, Eating Habits, and Motivation to Change towards a Healthier Life-style

Regarding smoking habits, only 10% of the participants (n = 4) were current smokers, and almost all of the men interviewed were aware that smoking was a risk factor for several health conditions, respiratory diseases in particular. Most participants consumed alcohol: 52.5% were moderate drinkers, while 37.5% were high-risk drinkers. Regarding alcohol consumption, 42.5% of the participants believed that alcohol negatively impacts on health, while 20% did not know the effects of alcohol on health, and 22.5% believed that moderate alcohol consumption has no influence on their own health status. Some individuals (15%) declared that a moderate intake of alcohol had a positive impact on their health.

Almost all participants (97.5%) were aware of the effects of a healthy diet on physical fitness, 45% were aware they were overweight or obese, and 40% declared the appropriateness of improving their eating habits.

Overall, almost all men participating in this study would not change their smoking, alcohol drinking, and/or eating habits (87.5%), and the pros and cons of change were not defined by 72.5% and 62.5% of participants, respectively. Data are presented in Supplementary material Table S4.2.

Among the men who do not meet the current PE recommendation, 32.5% were in the precontemplation stage, and thus not willing to engage in exercise. However, 17.5% were in the contemplation stage, and one man was in the preparation stage. Among the 10% of current smokers, one was in the contemplation stage, i.e., willing to quit. Similarly, among the 37.5% of high-risk drinkers, one was willing to reduce his alcohol consumption. Finally, among the 40% of participants that recognized that their diet should be improved, three individuals were in the contemplation stage, and one was in the action stage because he had been following a diet to lose weight for six months. Data are presented in Table 4.3.

Table 4.3 Descriptive analysis of participants PE, smoking, alcohol drinking, and eating habits and the stages of change distribution.

Stage of change (TTM)	PE N (%)	Smoking N (%)	Alcohol drinking N (%)	Diet N (%)
Precontemplation	13 (32.5)	3 (7.5)	14 (35.0)	12 (30.0)
Contemplation	7 (17.5)	1 (2.5)	1 (2.5)	3 (7.5)
Preparation	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Action	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)
Maintenance	19 (47.5)	36 (90.0)	25 (62.5)	24 (60.0)

Abbreviations: TTM, transtheoretical model; PE, physical exercise.

DISCUSSION

The aim of this study was to describe the lifestyle of patients recently diagnosed with PCa, with specific focus on their PE habits and on motivation and perceived barriers to change. Despite the fact that most participants performed PE regularly and considered their lifestyle as sufficiently active, most did not meet the recommended level of PE. This finding confirms previous studies [221] and implies that men with PCa should be informed about the exercise dose, frequency, and intensity that are suitable to produce the desired benefits. In patients with cancer, the period of time immediately after diagnosis seems very appropriate to recommend adopting a healthier lifestyle that includes regular PE [236]. In fact, if cancer treatments can increase the barriers against exercise [113], the period immediately following diagnosis, before treatment begins, is a teachable moment to promote change [218]. During this teachable moment, health-care professionals, and especially oncologists, should convey clear and evidence-based recommendations to their patients [237], giving explicit information about the benefits of regular PE in counteracting the side effects of cancer treatments and in preventing cancer progression. On the other hand, men receive a lot of information at the time of diagnosis, and ongoing cancer-related symptoms, such as incontinence, may also act as a barrier to PE [219]. Therefore, men may be more interested in the curative effects of the recommended treatments and may be less receptive to other information about their health. In addition, a lack of time, a lack of resources, or poor counseling on exercise and accessible facilities may be perceived as barriers by both patients and clinicians [238]. These barriers should be overcome; accessible and appropriate resources should be promoted that clinicians could recommend to their patients.

Our results show that men who have been diagnosed with PCa experience personal, environmental, and social barriers to PE, the most common barriers being pain or discomfort, lack of willingness/interest, and work/family schedule interference. In contrast with previous studies [221,222], lack of time was reported by only about 22% of our participants. This discrepancy could be due to the fact that most of the participants were retired. In line with previous research, group exercise, supervised exercise, but also autonomously-based exercise, seem to act both as a motivational factor and a barrier, according to personal preferences [239]. In our sample, ageing acted as a barrier, which was consistent with previous research [240]. This result highlights the need for greater efforts to promote active aging, as also advocated by the global agenda [8].

A quite high proportion of patients declared that they would participate in a structured exercise program to improve their health status, and most of them already met the current guidelines for PE. Thus, people who exercise are probably aware of the benefits of PE; instead, a great effort must be made to help sedentary people change their lifestyle.

Men that would participate in a structured exercise program mostly stated their preferences regarding the type of exercise they would like to engage in, and few individuals excluded a priori any type of physical activity, such as impact exercise or jogging, because they were thought to be potentially harmful on the musculoskeletal system. Also, some participants stated they would not like to exercise at a gym, in contrast with results of previous studies [222] and considered outdoor activities and the landscape as a facilitator for engaging in PE. As expected, the participants in this study considered the physician’s recommendation to exercise a motivational factor, but the evidence suggests that treating physicians do not regularly advise patients with PCa to exercise [241]. Since patients with PCa can exercise safely at the appropriate moderate-high intensity, health-care professionals should endorse adopting regular PE for patients with PCa [228].

This study also describes the main barriers to exercise manifested by our sample, which are in line with other studies [222]. It is important for health-care professionals to understand the potential objective and subjective barriers to practicing regular PE in order to support patients in overcoming them. Moreover, the recommended exercise should be as aligned with the patient's preferences as possible to prevent loss of interest and withdrawal [222].

This study revealed that newly diagnosed patients with PCa seem unmotivated to change their smoking, alcohol drinking, and eating habits and also revealed a certain degree of unawareness of the role of lifestyle in the prevention and management of cancer. In fact, although several individuals in the sample examined were overweight or even obese, most considered their lifestyle habits as fairly good, and almost 18% of them underestimated their weight. Also, most patients did not know the effects of alcohol on their health or that 2 units/day of alcohol is the recommended limit for alcohol use in men [234], and those who exceeded that limit did not consider themselves as high-risk drinkers. On the other hand, a recent Italian study showed that more than half of cancer patients changed their diet and stopped drinking alcohol since their diagnosis [242]. These discrepancies in results could be explained by the older average age and the low education level of the sample we investigated, as data collected on the Italian population seem to confirm that alcohol consumption is higher in the older population and in those with a lower education level [243]. Thus, educating men with PCa on the risks associated with unhealthy behaviors is fundamental, as it facilitates the adoption of a healthier lifestyle that includes regular PE to reduce the side effects of cancer treatments and to improve quality of life [5].

This study has some limitations. First, due to the current pandemic, we did not reach the expected sample size, and the sample recruited was not large enough to be representative of the target population. Moreover, the response rate was relatively low (51.9%) compared to that of a similar recent study (88.3%) [242]. Thus, it is possible that participants were particularly interested in the topic of the research, limiting the generalizability of the findings. Moreover, the data were collected through a non-validated interview, which collected self-reported data on PE level, smoking, alcohol drinking, and eating habits, which may not objectively represent the patients' lifestyle. Therefore, there is a potential risk of biased responses, since it is well known that self-reporting of behaviors in surveys may lead to biased estimates of the positive, socially desirable behaviors [244,245]. Nevertheless, our data were collected through questions that have already been used in several national surveillance systems [234,235]. Finally, this study did not investigate the role of a life partner, who, based on previous studies, may support men with PCa to adopt and maintain healthy behaviors [246].

CONCLUSIONS

To conclude, the results of this study highlight the importance of health promotion interventions targeting patients that have recently been diagnosed with PCa, since nearly a half of our participants did not meet the recommended level of PE for cancer survivors, but a relevant portion of the same would participate in a structured exercise program. Health-care professionals should provide information about behavioral risk factors, particularly alcohol drinking and eating habits, and about the numerous health benefits that can be obtained by performing the recommended dose of exercise. With this specific aim, public health measures should be implemented, including education starting in primary or secondary schools on how lifestyle behaviors impact health, as healthy behaviors are an essential part of cancer prevention. Importantly, environmental and policy barriers need to be addressed to increase the sustainability and accessibility of PE interventions. Moreover, health-care professionals should apply appropriate strategies to support patients in overcoming barriers to PE and engage in long-term enjoyable and feasible PE. Future research is required to verify the feasibility and effectiveness of PE programs that consider patients' preferences in terms of exercise in order to maximize the effectiveness of PE through sustained virtuous behavior.

STATEMENTS AND DECLARATIONS

Funding

The authors declare that no funds, grants, or other support were received.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Comitato Etico dell'Area Vasta Emilia Nord (05/06/2019, number 425/2019/OSS/AUSLRE).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

Not applicable

Availability of data and materials

Data set generated and analyzed in the current study was managed by the Information and Technologies Service (STIT) of the Azienda USL-IRCCS of Reggio Emilia in order to protect patient privacy. The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIALS

Table S4.1 Interview.

Sociodemographic factors
1. What is your marital status?
2. Who do you live with?
3. What is your level of education?
4. What is your employment status and what kind of work do you do (sedentary, active, partially active)?
5. What mode of transport do you usually use?
PE level, habits, and preferences
6. Do you exercise regularly? 7. What kind of physical exercise do you usually do? 8. How much physical exercise do you get per week? 9. How important is it to you to exercise? 10. Why is it important/not important? 11. What satisfies you about exercising?
Regarding exercising perceived barriers, facilitators and motivation to change
12. How do you feel about including regular physical exercise among your habits? If this is not feasible, why not? 13. What would make including physical exercise feasible? 14. How do you think it would help you to improve your health? 15. What are the barriers against your doing physical exercise? 16. What are the facilitators that help you to exercise? 17. If proposed, would you participate in a long-term structured physical exercise program? Why?
Smoking, alcohol drinking, and eating habits
18. Do you smoke? 19. Have you ever smoked in the past? 20. How many cigarettes do you smoke a day? 21. How many years have you been smoking? 22. Have you ever thought about quitting smoking? 23. How do you feel about quitting smoking? 24. How do you think smoking can affect your health? 25. Do you drink alcohol? 26. How often you drink alcoholic drinks? 27. How do you think drinking alcohol can affect your health? 28. Are you satisfied with your eating habits? 29. What foods are you unwilling to give up ? 30. How do you feel about your weight? 31. How important is it to you to feel good/fit? 32. Do you think you could improve anything in your eating habits to feel better?
Motivation to change and perceived barriers towards a healthier lifestyle
33. Is there anything you would change in your lifestyle? If so, what would you like to change in your lifestyle? 34. What do you think the disadvantages of making this change may be? 35. What do you think the benefits of this change to your health status may be? 36. How important is it to you to change this habit?
Perception of cognitive status
37. Do you have any difficulties performing activities of daily life, for example going grocery shopping, looking after a grandchild, cooking, driving a car, etc.? 38. Do you have any memory issues? 39. In what kind of situations do you have memory issues? 40. How do you feel about learning new things?

Table S4.2 Descriptive analysis of participants by PE level, and motivation to change smoking, alcohol drinking, and eating habits.

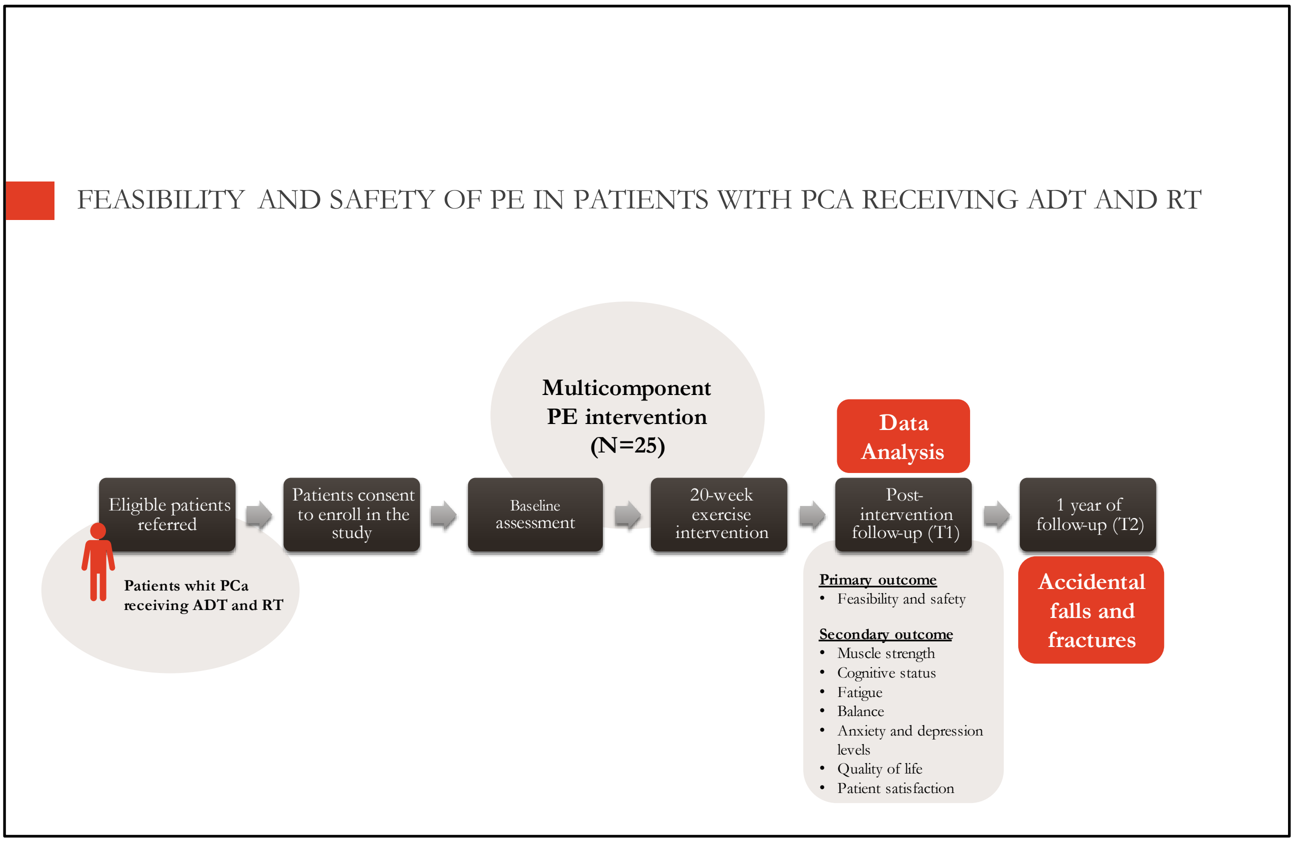
		Total	Not meet aerobic PE guidelines	Meet aerobic PE guidelines
		N (%)	**N (%)**	**N (%)**
		40 (100.0%)	21 (52.5)	19 (47.5)
Smoking habits				
Smoking category	Not a smoker	17 (42.5)	9 (52.9)	8 (47.1)
	Former smoker	19 (47.5)	9 (47.4)	10 (52.6)
	Smoker	4 (10.0)	3 (75.0)	1 (25.0)
Smoking's impact on one's health	It's unhealthy	35 (87.5)	19 (54.3)	16 45.7)
	Not affect	3 (7.5)	2 (66.7)	1 (33.3)
	Not sure	2 (5.0)	0 (0.0)	2 (100.0)
Alcohol drinking habits				
Alcohol consumption	Moderate drinker	21 (52.5)	10 (47.6)	11 (52.4)
	High-risk drinker	15 (37.5)	10 (66.7)	5 (33.3)
	Nondrinker	4 (10.0)	1 (25.0)	3 (75.0)
Impact of alcohol consumption on one's health	It's unhealthy	17 (42.5)	7 (41.2)	10 (58.8)
	It's healthy	6 (15.0)	3 (50.0)	3 (50.0)
	Not affect	9 (22.5)	6 (66.7)	3 (33.3)
	Not sure	8 (20.0)	5 (62.5)	3 (37.5)
Eating habits				
Eating habits satisfaction	Yes	35 (87.5)	20 (57.1)	15 (42.9)
	No	5 (12.5)	1 (20.0)	4 (80.0)
How do you feel about your body weight?	I feel good/in shape	22 (55.0)	9 (40.9)	13 (59.1)
	I feel overweight/heavy	17 (42.5)	11 (64.7)	6 (35.3)
	I feel bad/obese	1 (2.5)	1.0 (100)	0 (0.0)
Relevance of physical fitness	Quite/very important	39 (97.5)	21 (53.8)	18 (46.2)
	Not very /not important	1 (2.5)	0 (0.0)	1 (100.0)
Is there anything you would like to improve?	No	24 (60.0)	13 (54.2)	11 (45.8)
	Yes	16 (40.0)	8 (50.0)	8 (50.0)
Motivation to change smoking, alcohol drinking, and eating habits				
Is there something you would like to change in your lifestyle?	No	35 (87.5)	19 (54.3)	16 (45.7)
	Yes	5 (12.5)	2 (40.0)	3 (60.0)
Cons of change[a]	Not sure	13 (32.5)	7 (53.8)	6 (46.2)
	None	12 (30.0)	4 (33.3)	8 (66.7)
	Requires diligence/organizational skills	7 (17.5)	3 (42.9)	4 (57.1)
	Stress/fatigue	5 (12.5)	3 (60.0)	2 (40.0)
	Change my habits / take time away from something else	5 (12.5)	4 (80.0)	1 (20.0)
	Useless sacrifices	3 (7.5)	2 (66.7)	1 (33.3)
	Mnemonic difficulties	1 (2.5)	1 (100.0)	0 (0.0)
Pros of change[a]	None	25 (62.5)	13 (52.0)	12 (48.0)
	Physical wellbeing	8 (20.0)	5 (62.5)	3 (37.5)
	Not sure	4 (10.0)	3 (75.0)	1 (25.0)
	Psychological wellbeing	4 (10.0)	3 (75.0)	1 (25.0)
	Improved health	2 (5.0)	0 (0.0)	2 (100.0)
Relevance of change	Not very/not important	36 (90.0)	20 (55.6)	16 (44.4)
	Quite/very important	4 (10.0)	1 (25.0)	3 (75.0)

Abbreviations: PE, physical exercise.
[a]Multiple responses were possible.

CHAPTER V

Experimental study

Feasibility and safety of physical exercise in men with prostate cancer receiving androgen deprivation therapy and radiotherapy: a study protocol[d]



[d] Preprint version of the manuscript submitted and under revision to *BMJ Open*.

Barbara Bressi[1,2], Cinzia Iotti[3], Maribel Cagliari[4], Silvio Cavuto[5], Stefania Fugazzaro[2] & Stefania Costi[4,6].

Affiliations:

[1]PhD Program in Clinical and Experimental Medicine, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Reggio Emilia, Italy.
[2]Physical Medicine and Rehabilitation Unit, Azienda USL–IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[3]Department of Oncology and Advanced Technologies, Radiotherapy Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[4]Department of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy.
[5]Research and Statistics Infrastructure, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.
[6]Scientific Directorate, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.

ABSTRACT

Introduction: Androgen deprivation therapy (ADT) and radiotherapy (RT) increase survival in selected patients with prostate cancer (PCa). Nevertheless, the side effects of these therapies are associated with an increased risk of accidental falls and fractures and a decreased quality of life. Preliminary evidence suggests that physical exercise (PE) can be a valid strategy to reduce the side effects of ADT and RT in men with PCa. Despite this knowledge, most patients with PCa are insufficiently active, and there is a lack of data on the safety and adherence to the recommended dose of PE. This study protocol is designed to examine the feasibility and safety of a multicomponent experimental PE intervention targeting psychophysical and cognitive functions and the quality of life in this population.

Methods and analysis: This is a pilot feasibility study. Twenty-five men currently treated with ADT and RT for PCa will be invited to participate in a 20-week, multicomponent PE intervention, including supervised and unsupervised exercise sessions and meeting the current recommendation for exercise in cancer. The primary outcomes are PE feasibility (recruitment, adherence, and drop-out rates) and safety (adverse events related and unrelated to the intervention). The secondary outcomes are muscle strength, balance, fatigue, symptoms of anxiety and depression, cognitive function, quality of life, and patient satisfaction. We will also record the number of accidental falls and fractures occurring during the intervention and at one year of follow-up.

Ethics and dissemination: The study has received ethics approval from The Area Vasta Nord Local Ethics Committee (Province of Reggio Emilia, June 23, 2020, Number 520/2020/SPER/IRCCSRE). Recruitment began in September 2020 and will be completed in September 2021. The results will be disseminated through scientific journals and conference presentations.

Trial registration: ClinicalTrial.gov (NCT04500080)

Keywords: Prostatic neoplasms, Accidental falls, Bone fractures, Exercise, Androgen deprivation therapy, Radiotherapy.

Strengths and limitations of this study

- This pilot study thoroughly assesses the feasibility and safety of a multicomponent experimental PE intervention for individuals with PCa receiving ADT and RT.
- Preliminary data regarding the efficacy of structured, supervised, and unsupervised aerobic, resistance, neuromotor, and impact-loading exercise on the bone health of this population will be provided.

- Both the ecological setting, a community sport facility, and the step-down approach, from supervised to unsupervised PE intervention, should foster the adoption of exercise as daily habits, promoting healthy behaviour.
- The single-group design does not allow for assessment of the efficacy of the multicomponent experimental PE intervention on the bone health outcomes of interest.

INTRODUCTION

Prostate cancer (PCa) affects approximately 3.7 million people worldwide, ranking first among the most prevalent cancers in the male population [2]. Curative treatment of locally advanced PCa usually entails radiotherapy (RT) frequently associated with androgen deprivation therapy (ADT) [22]. This type of multimodal treatment is unfortunately associated with a large number of side effects [5,247]. Previous studies have demonstrated a significant increase in cancer-related fatigue in patients receiving RT, which not only decreases physical well-being but also affects daily activities, cognitive function, and quality of life [248–250]. Furthermore, it is well known that the cardiovascular, metabolic, cognitive, and musculoskeletal adverse effects of ADT lead to an increased number of accidental falls and fractures in this population [31]. Furthermore, since PCa incidence increases with age [2], older patients are normally already at a greater risk of frailty due to the presence of other comorbidities that can dramatically affect physical function [251]. Physical exercise (PE) interventions can prevent a large number of these complications, improving the health and quality of life of individuals with PCa [10,252]. These PE programs should include moderate-high intensity activities that must be performed regularly to maintain exercise-related benefits [79,88]. A recent systematic review of randomized controlled trials (RCTs) showed that to counteract the negative effects of ADT on bone, multicomponent PE interventions involving aerobic, resistance and impact-loading exercise have been performed [194]. Although these interventions were feasible for most participants in the RCT, those study protocols did not systematically record the adherence rate or adverse events associated with the experimented PE interventions [81,88,228]. However, these data are fundamental to fostering individual compliance with the recommended dose of exercise [81]. In fact, despite the well-known benefits of PE for cancer survivors [79,81], this population is frequently unactive [219] and reports several common barriers to exercise, such as the location or distance to facilities [220,253,254]. Furthermore, hospital-based supervised PE interventions can be challenging to implement because they require the use of complex hospital resources [253,255,256]. This modality does not promote long-term adherence to PE or changes towards a healthier lifestyle, which are considered contemporary health priorities for physical therapy practice [257,258].

It is suggested that an intensive lifestyle program that includes dietary supplements, moderate aerobic exercise, stress management, and support group participation may affect the progression of PCa at the early stage [259]. Furthermore, a healthier lifestyle seems to be associated with a better health-related quality of life [260].

In this regard, we are investigating the lifestyle of patients recently diagnosed of PCa, their perceived barriers and facilitators to PE, and motivation to change towards healthier lifestyle (Bressi et al. Physical Exercise Habits, Lifestyle Behaviors, and Motivation to Change Among Men with Prostate Cancer: A Cross-Sectional Study. Unpublished Material). Therefore, based on previous research and our current descriptive study, we developed a structured experimental PE intervention that combines supervised and unsupervised exercise with a step-down approach. This PE intervention is implemented in a community sports facility and is currently being tested in a small group of patients with PCa receiving ADT and RT for feasibility and safety. Secondary outcomes include muscle strength, balance, fatigue, symptoms of anxiety and depression, cognitive function, quality of life and patient satisfaction. We will also record the number of accidental falls and fractures occurring during the intervention and at one year of follow-up. This study protocol describes the experimental PE intervention in detail, with related outcomes, to allow for reproducibility and adaptation to other contexts.

METHODS

Patients and study design

This single group feasibility pilot study was approved by the Comitato Etico dell'Area Vasta Emilia Nord (June 23, 2020, Number 520/2020/SPER/IRCCSRE) and was registered with ClinicalTrials.gov (Identifier NCT04500080). This study protocol adheres to the recommendation for clinical trials (SPIRIT) guidelines, and the study registration data set is shown in Table 5.1 [261]. Eligible patients are adult men (≥18 years) with a histological diagnosis of PCa who are currently treated with ADT and RT and are able to communicate in the Italian language. Participants with musculoskeletal, cardiovascular, psychiatric, or neurological disorders that contraindicate exercise will be excluded. All patients referred to RT which are also candidate to receive ADT will be assessed for eligibility. If confirmed, written informed consent will be obtained from all participants, who will be invited to participate in a 20-week structured, supervised and unsupervised, multicomponent PE program. Patients will be assessed at baseline (T0), at the end of the intervention (T1), and at follow-up, which will occur 12 months from recruitment (T2).

So, the experimental PE intervention will start concomitantly with RT, which lasts about two months. As regard to ADT, its duration can vary from six to thirty-six months, and it can begin up to three months before a patient's enrolment in this study and RT commencement.

Table 5.1 Study registration data set.

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04500080
Date of registration in primary registry	August 5, 2020
Secondary identifying numbers	520/2020/SPER/IRCCSRE
Source of monetary or material support	Manodori Foundation
Primary sponsor	Azienda USL-IRCCS di Reggio Emilia
Secondary sponsor	NA
Contact for public queries	BB [barbara.bressi@ausl.re.it], SC [stefania.costi@unimore.it]
Contact for scientific queries	SC [stefania.costi@unimore.it], BB [barbara.bressi@ausl.re.it]
Public title	Feasibility and Safety of Physical Exercise in Men With Prostate Cancer (PCa_Ex)
Scientific title	"The Feasibility and Safety of Physical Exercise Program in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol"
Countries of recruitment	Italy
Health conditions or problems studied	Prostate cancer, androgen deprivation therapy and radiotherapy
Intervention	Physical exercise intervention
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: man
	<u>Inclusion criteria:</u> Adult male patient (≥ 18 years)
Study type	Interventional Allocation: single group assignment
Date of first enrolment	April 2021
Target sample size	25 patients
Recruitment status	Recruiting
Primary outcomes	Feasibility: recruitment, adherence, and drop-out rates Safety: any adverse events related and not related to the intervention
Key secondary outcomes	Muscle strength, fatigue, cognitive function, balance, quality of life, anxiety and depression level, and number of falls and fractures.

Recruitment strategies

Between September 2020 and September 2021, eligible patients treated by the Radiotherapy Unit of Santa Maria Nuova Hospital of Reggio Emilia (Italy) will be given brief, written information about the study by their attending physician (radiotherapist or oncologist). Upon written consent, patients willing to receive more information will be referred to the Physical Medicine and Rehabilitation Unit and will receive a phone call by a research staff member (physiotherapist), who describes the study aim and modalities to them in detail. Patients who confirm their interest in participating will receive written information and consent forms to participate in the study to be filled out and signed. They will also make the first appointment to provide written consent and to perform the baseline assessment. The patient recruitment process is shown in Figure 5.1.

Baseline assessment

In the baseline assessment, demographic, anthropometric, clinical data, and physical function data will be collected. Clinical data include the date of diagnosis, tumor stage, time since receiving ADT and RT, and the presence of comorbidities assessed through the Charlson Comorbidity Index (CCI) [233]. Physical function will be measured using a six-minute walk test (6MWT) [262] to calculate the intensity of aerobic exercise.

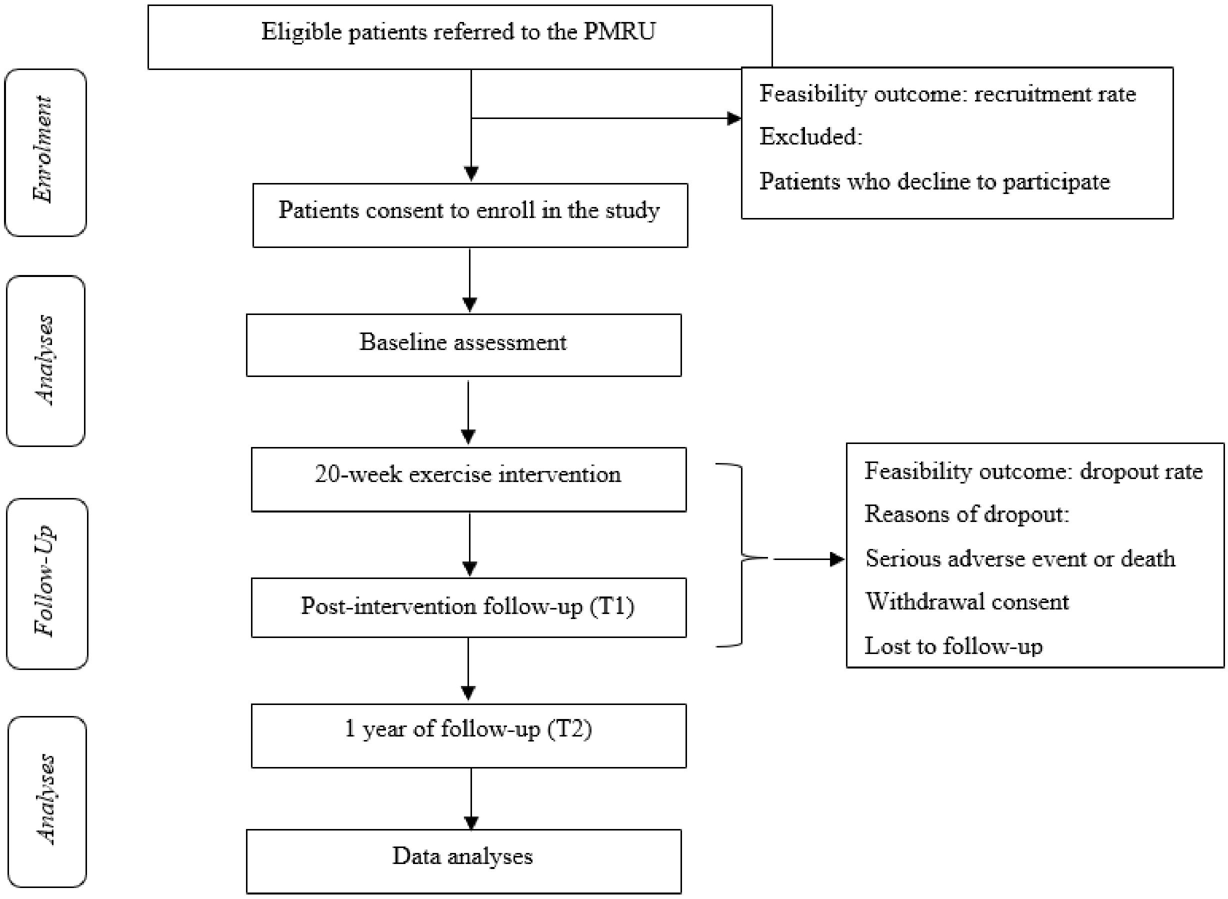
Experimental PE intervention

The multicomponent experimental PE intervention will last 20 weeks and consists of supervised and unsupervised exercise sessions held three times per week. Following a step-down approach, during the first eight weeks, all PE sessions will be supervised by a physiotherapist, while during the following four weeks, only one weekly session will be supervised, whereas the other two will be unsupervised; finally, during the last eight weeks of experimental PE, all sessions will be unsupervised. Supervised sessions will be conducted in small groups or individually at the Municipal Athletics Field in Reggio Emilia according to scheduled appointments, whereas the unsupervised sessions can be completed by participants in times, modalities and places of their convenience, providing for them the possibility to access the Municipal Athletics Field.

The multicomponent PE intervention meets the dictates for exercise components, posology (frequency, sets, repetitions, intensity) and progression recommended for healthy adults [142]. Its components are aerobic, resistance, core muscle stabilization, and neuromotor exercises associated with cognitive tasks. In addition, exercise intervention will include impact-loading exercise to provide an effective bone osteogenic stimulus. This type of exercise has been considered an effective strategy to prevent loss of bone mineral density (BMD) in elderly patients [41,56] and has been applied in patients with PCa receiving ADT in previous studies [194]. Altogether, the components of this intervention should preserve muscle strength and improve fatigue, balance, and cognitive function [142], and eventually, it should prevent accidental falls and fractures.

The intervention is tailored to individual general health, functional capacity and, as far as possible, preferences.

Figure 5.1 Schematic study flow diagram.



Abbreviations: PMRU= Physical Medicine and Rehabilitation Unit

Supervised PE sessions

Supervised sessions last one hour and 15 minutes and include a period of warm up and cool-down and a combination of the following PE components:

• Aerobic exercise consists of 20-30 minutes of aerobic activity at moderate-high intensity, from 60 to 80% of maximum heart rate (% HRmax), previously determined through the 6MWT [262], which is conducted according to the current guidelines [263]. To obtain the greatest effects on bone health, the proposed aerobic exercise activities are walking or jogging, depending on individual capacity and habitual or previous experiences of physical activity. The perceived effort will be monitored by the Borg's Rate of Perceived Exertion scale (RPE) to maintain it between fairly light to hard, which corresponds to RPE scores 11 to 15 [264]. To ensure that participants reach the target HR, we will use HR monitors.

• Progressive resistance exercise consists of strength activity of the major lower and upper extremity muscle groups, using body weight as a load and free weights (resistance bands, dumbbells, anklets with weight, medicine ball). During each session, the goal is to perform four to eight exercises targeting different muscle groups by performing two to four sets of 8-15 repetitions for each exercise. The perceived effort will be measured by the individual using the Borg RPE scale [265] (score between 11 and 15). The progression of intensity will be provided, starting the exercises with body weight and gradually increasing the load using free weights [266]. Adjustments to load will be made when participants can complete the highest number of specified repetitions (≥ 15 repetitions, see also Table 5.2). Thus, the number of exercises, dose progression (sets, repetitions) and related difficulties (e.g., squat depth and/or duration, double task exercises) will be changed during the weeks based on the patient's compliance and performance (see also Table 5.2). For isometric exercises, dose will be incrementally increased by adding free weights, further limb exercise or asking for double task exercise, and/or increasing the duration of exercise from 20 to 60 seconds.

• Core muscle stabilization exercise consists of postural and trunk stability exercises (e.g., strengthening of transverse abdominis and pelvic floor muscles). Participants will perform two core exercises per session in two-four sets of 8-15 repetitions. Sets, repetitions, additional free weights, additional upper body and/or lower body movements and time of exercise from 20 to 60 seconds will be used to increase the intensity of exercises.

• Neuromotor exercise consists of balance and functional (coordination) exercises associated with cognitive tasks (e.g., counting, adding, subtracting, saying day of weeks) and includes fit ball exercises (e.g., knee and contralateral upper limb extension sitting on fit ball), standing balance activities (e.g., stand on one leg) and dynamic functional tasks (e.g., stop walking balanced on one foot, walking backward). Participants will be asked to complete two to four static and dynamic exercises per session. Static exercises are performed in two-four sets of 20-60 seconds, while dynamic exercises are performed in two-four sets of 8-15 repetitions. To provide progression, exercises are modified by introducing difficulties (e.g., closing eyes, reducing base of support, introducing unstable support, adding free weights, or adding a second cognitive or manual task).

• Impact-loading exercise consists of jumping, leaping, jumping rope, hopping on one leg, going up and down steps, etc., in other words, exercises that provide impact with the ground using the body weight as a load. Two to four exercises per session will be performed. Training intensity is increased by adding repetitions, additional free weights, introducing multidirectional movement, and raising the exercise speed. To provide a large number of stimuli, several tools will be used.

Also, for core muscle stabilization, neuromotor, and impact-loading exercises, adjustments to load will be made when participants can complete the highest number of repetitions (≥15 repetitions) at the target exertion (RPE score between 11 and 15).

A detailed description of exercises, posology, tools, and progressivity is available in Table 5.2. Altogether, progressive resistance, core muscle stabilization, neuromotor, and impact-loading exercises are performed for 30-40 minutes each session.

Table 5.2 Description of exercise program and dose progression.

Weeks		**1-4**	**5-8**	**9-12**	**13-16**	**17-20**
Component	**Dose**					
Aerobic exercise	Intensity (% HRmax)	60-80%	60-80%	60-80%	60-80%	60-80%
	Duration	15-20 min	20 min	20 min	25 min	30 min
Progressive resistance exercise	Sets	2	2	3	3	4
	Repetitions	8-12	12-15	8-12	12-15	8-12
	Difficulties	Additional free weights, range of motion, number and time* of exercise, additional upper body and/or lower body movements				
	Materials	Free weights (resistance bands, dumbbells, anklets with weight, medicine balls), step				
Core muscle stabilization exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Additional free weights, additional upper body and/or lower body movements and time* of exercise				
	Materials	Free weights (resistance bands, dumbbells, anklets with weight, medicine balls), fit ball				
Neuromotor exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Time* of exercise, closing eyes, reducing base of support, introducing unstable support, adding free weights, or adding a second cognitive or manual task				
	Materials	Free weights (dumbbells, anklets with weight, medicine balls), fit ball, balance board				
Impact-loading exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Additional free weights, introducing multi-directional movement, and raising the exercise speed				
	Materials	Free weights (dumbbells, anklets with weight, medicine balls), hurdles/hoops/training cone markers, rope, steps				

Abbreviations: % HRmax, percent maximum heart rate.
*varies from 20 to 60 seconds and regards isometric exercise and static balance exercise

Unsupervised PE sessions

Unsupervised sessions also consist of all exercise components. In addition to walking or jogging, aerobic exercise can also be performed using bikes, stationary bikes, or other aerobic activities based on individual availability and preferences. Regarding the progressive resistance, core muscle stabilization, neuromotor, and impact-loading exercise components, exercises that trade on body weight or with resistance bands that will be provided to patients are taught and suggested to overcome the possible unavailability of appropriate tools. Each activity and exercise will be explained to participants and practiced by them during the supervised sessions. Furthermore, written educational material (Appendix II) with instructions and pictures of the exercises will be provided to maximize accuracy of the unsupervised execution. The physiotherapist provides individualized indications regarding the activities to be performed during unsupervised sessions but also supports participants in progressively increasing the exercise workload when the individual perceives an improvement in their functional capacity.

Outcome measures

Primary outcome

Feasibility will be measured through recruitment, adherence, and dropout rates.

The recruitment rate is the proportion of eligible individuals referred to the Physical Medicine and Rehabilitation Unit by their treating physician included in the study.

Protocol adherence is the proportion of exercise sessions that are attempted and completed by each participant. The percentage of patients who withdraw from the study and their reason for withdrawal will also be registered.

Safety is measured through the recording of any adverse events related and not related to PE and its grading for seriousness [267], causality and health consequences by the researcher during the study.

Feasibility and safety are monitored by the physiotherapist through direct inquiry during the first 12 weeks of the program when supervised sessions are implemented and through a weekly phone call during the last eight weeks of unsupervised sessions.

Secondary outcomes

Secondary outcome measures include changes in muscle strength, fatigue, cognitive function, balance, quality of life, symptoms of anxiety and depression, number of accidental falls and associated fractures, and participant satisfaction.

Muscle strength

The strength of the major lower and upper extremity muscle groups will be measured with the 10-RM test (extensor muscle group). The 10-RM test assesses the maximum weight that can be lifted for ten repetitions while maintaining the correct technique. Prior to attempting this test, participants will complete five minutes of aerobic warm-up and 1-2 sets of 15-20 repetitions with a light load. Then, the load will be progressively increased while the number of repetitions will decrease accordingly until only ten repetitions can be completed. A recovery period of two minutes will be provided between each set [268,269].

Fatigue

Fatigue will be measured using the Fatigue Severity Scale (FSS), a 9-item questionnaire on how fatigue interferes with activities and that rates its severity. The item is scored on a 7-point Likert scale with 1 = strongly disagree and 7 = strongly agree. The minimum score = 9, and the maximum score = 63. A higher score indicates greater fatigue severity [270].

Cognitive function

Cognitive function will be measured using the Mini Mental State Examination (MMSE), a brief cognitive test designed to assess the overall cognitive status of patients. The MMSE tests five areas of mental status (orientation; registration; attention and calculation; recall; language) and is scored on a scale of 30, with adequate cognition for most adults indicated by scores from 24 to 30 [230].

Balance

Balance will be measured using the Tinetti Performance Oriented Mobility Assessment (POMA). The Tinetti POMA scale is a clinical test used to measure balance and gait abilities. The balance section (POMA-B) consists of 9 items, while the gait section (POMA-G) consists of 8 items. Each item can receive an ordinal score from 0 to 2, where "0" indicates the highest level of impairment and "2" indicates individual independence. The maximum possible total score for POMA-T is 28, for POMA-B is 16, and for POMA-G is 12. A POMA-T cut-off score < 19 indicates a high risk of falling [271,272].

Quality of life

Quality of life will be measured using the Short Form-12 questionnaire (SF-12), which consists of twelve items measuring different physical and mental health parameters. Higher scores indicate better physical and mental health [273].

Anxiety and depression level

Anxiety and depression level will be measured using the Hospital Anxiety and Depression Scale (HADS), a fourteen-item scale equally distributed across anxiety and depression states. The total score ranges from 0-21, with higher scores indicating greater levels of mood disturbances. In patients with cancer, a cut-off score of > 9 for the HADS-A and > 7 for the HADS-D indicates clinically relevant anxiety and depression levels, respectively [274].

Accidental falls and fractures

During the intervention, accidental falls and fractures were recorded directly by the physiotherapist who supervised the sessions and performed the weekly phone call and thereafter at the 12-month follow-up.

Participant satisfaction

Patient satisfaction will be assessed through a simple structured interview. At the end of the intervention, each participant will be invited to answer the following four open-ended questions that investigate its acceptability:

- How do you assess the overall experience you have had by participating in this study?
- Which activities did you like the most?
- Which activities did you like least?
- What can be improved in your opinion, or what would you have liked to have been offered?

A summary of the outcome measures and their assessments at follow-up is shown in Table 5.3.

Table 5.3 Data collected.

Variables	**Data collection method**	**Data collection points**		
		Baseline	T1 (20 weeks*)	T2 (1 year*)
Primary outcome measures				
Feasibility	Recruitment rate Adherence rate Drop-out rate	x	 x x	
Safety	Number and type of AEs related and not related to intervention		x	
Secondary outcome measures				
Muscle strength	Ten repetitions maximum (10-RM) Test	x	x	
Fatigue	Fatigue Severity Scale (FSS)	x	x	
Cognitive function	Mini mental State examination (MMSE)	x	x	
Balance	Tinetti Performance Oriented Mobility Assessment (POMA)	x	x	
Quality of life	Short form-12 questionnaire (SF-12)	x	x	
Anxiety and depression level	Hospital Anxiety and Depression Scale (HADS)	x	x	
Numbers of fall and fractures	Recorded directly by the physiotherapist during the supervised sessions and with weekly phone call during unsupervised session	x	x	x
Participant satisfaction	Patient satisfaction		x	
Additional measures	Anthropometry (height, weight, BMI) Demographic data Clinical data Functional capacity (6MWT)	x x x x	x	

***Abbreviations*:** AEs, adverse events; BMI, body mass index; 6MWT, six minutes walking test.
*from baseline.

Sample size calculation

No formal sample size requirement is needed for this single-group, pilot, feasibility study. At the Santa Maria Nuova Hospital of Reggio Emilia, nearly 30 patients/year undergo ADT and RT, and we aim to recruit 25 patients during the 12-month recruitment period.

Data analysis

All statistical analyses will be performed by the local Clinical Trials and Statistics Unit of the AUSL-IRCCS of Reggio Emilia. The SAS System or R software will be used according to their availability at the time of data analyses. Descriptive statistics will be reported for feasibility and safety outcomes. For each percentage, the exact two-sided confidence interval will be calculated according to the Clopper-Pearson approach, ensuring a confidence level of at least 95%. In fact, since it is an exact technique, the confidence level typically does not coincide with 95%, the discrepancy for small samples being more noticeable. Adverse events will be described and grouped into homogeneous classes. The data regarding patient satisfaction will be analyzed to identify patterns of response and grouped into categories emerging from the data.

Descriptive statistics for secondary outcomes will be reported to inform potential future studies in terms of clinical health outcome measures. For all variables, percentiles, minimum, maximum, mean, and SD will be calculated. For the mean, a 95% two-sided confidence interval will be calculated assuming a t distribution. The changing over time of the secondary outcomes will be studied by the analysis of variance for repeated measures.

Concerning the number of accidental falls and fractures, as counts, the confidence interval for the mean will be calculated according to the Poisson distribution. No missing data imputation techniques have been planned, therefore only the available data will be analyzed. However, missing data will be appropriately described in their distributional aspects of relevance.

Data management and archiving

The dataset will be stored on a password-protected computer and managed by the Information and Technologies Service (STIT) of the Azienda USL-IRCCS of Reggio Emilia to protect patient privacy and data.

Patient and public involvement

Patients will participate in the study design so that the time and spaces necessary for the home-based intervention can be adapted according to their availability and discretion. Participants may suggest changes related to the frequency and intensity of the sessions and inform the study team about which type of exercises they prefer.

ETHICS AND DISSEMINATION

This study was approved by the Area Vasta Nord Local Ethics Committee of Azienda USL-IRCCS of Reggio Emilia (June 23, 2020, Number 520/2020/SPER/IRCCSRE), which will also review potential modifications, if any. All patients will provide consent prior to participation. Results will be disseminated through scientific peer-reviewed journals and conference presentations. The expected impact for this study is the development of a useful and acceptable PE program integrated into the daily routine of patients with PCa receiving ADT and RT.

These results will inform which type of PE is required to improve adherence to the recommended exercise guidelines for cancer survivors and will help researchers plan feasible PE interventions whose efficacy on bone health is to be verified through well-designed RCTs.

CHAPTER VI

Discussion

This chapter summarizes the findings from the two literature reviews and the observational study presented in the previous chapters and highlights future areas of research in the field of exercise and PCa that are warranted.

These results represent the first part of a research project whose goal was to investigate the effectiveness of PE in preventing BMD loss and accidental falls and fractures in patients with PCa receiving ADT. This thesis investigated the feasibility and safety of PE conducted with appropriate volumes and intensity to produce beneficial effects on bone health. In addition, it aimed at investigating the lifestyle of PCa patients at the time of diagnosis and their motivation for undertaking a healthier lifestyle, with particular regard to the adoption of regular PE.

As mentioned in the Introduction section (Chapter I), men with PCa receiving ADT experience several side effects, which impact their quality of life [5]. Although previous studies investigated the beneficial effects of PE on healthy men and the potential relationship between exercise and ADT [9,144], our first systematic review shows that the evidence on the effectiveness of PE on bone health in men with PCa on ADT is still lacking: PE might counteract BMD loss, but the evidence is inconsistent. Moreover, the effectiveness of PE on reducing the risk of accidental falls and fractures has not yet been investigated.

Regarding the effects of PE on BMD, two RCTs showed initial proof of prevention of BMD loss [151,155]. In these trials, the experimental PE consisted in resistance and impact-loading exercise or football training performed 2-3 times a week for at least 6-8 months. Bone remodelling, in fact, is favored by long-lasting mechanical loading, which may be achieved through PE [41]. The deformations on bone induced by PE activate the osteogenesis and reduce the osteoclastic processes [58,60,70]. To obtain an osteogenic stimulus, bone must be subjected to a strain higher than a threshold determined by the habitual strain range [61,63]. Thus, despite the inconsistency of the evidence, it is plausible that an intensive PE program that becomes part of the lifestyle of individuals with PCa receiving ADT might prevent BMD loss, thereby preventing fractures associated with accidental falls.

Moreover, it is well known that smoking, excessive alcohol consumption, and inadequate eating habits contribute to an increased risk of fractures due to osteoporosis [275]. Since osteoporosis is a common side effect of ADT in patients with PCa [34], a healthy lifestyle should also be recommended in this population.

The cross-sectional study conducted in the province of Reggio Emilia highlighted several barriers perceived by men newly diagnosed with PCa when considering a change toward a healthier lifestyle.

Nevertheless, the literature shows that the appropriate moment to recommend adopting a healthy lifestyle, including regular PE, seems to be immediately following a diagnosis of cancer [236]. In fact, if beginning cancer treatment can increase the barriers against PE [113], the period immediately following diagnosis, before treatment begins, can be a teachable moment to promote change [236]. This goal can be facilitated by educating the patients on the role of regular PE and the importance of a healthy lifestyle in the prevention of cancer progression and the side effects of treatment [79,81]. This is especially useful when this recommendation comes from the healthcare professionals, especially the oncologists, through clear, evidence-based messages [237]. In fact, despite the fact that most participants performed PE regularly and considered their lifestyle as sufficiently active, most did not meet the recommended level of PE.

This study revealed that men newly diagnosed with PCa seem unmotivated to change their smoking, alcohol drinking, and eating habits and also revealed a certain degree of unawareness of the role of lifestyle in the prevention and management of cancer. Although several individuals in the sample examined were overweight or even obese, most considered their lifestyle habits as fairly good, and almost 18% of them underestimated their weight. Also, most patients did not know the effects of alcohol on their health or that 2 units/day of alcohol is the recommended limit for alcohol use in men [216], and those who exceeded that limit did not consider themselves high-risk drinkers.

These results could be explained by the older average age and the low education level of the sample investigated, as data collected on the Italian population seem to confirm that alcohol consumption is higher in the older population and in those with a lower education level [243]. Thus, educating men with PCa on the risks associated with unhealthy behaviors is fundamental, as it facilitates the adoption of a healthier lifestyle that includes regular PE to reduce the side effects of cancer treatments and to improve quality of life [5].

As physiotherapists, we should endorse the adoption of regular PE for cancer survivors, including patients with PCa, as it is well tolerated and safe, even when performed at moderate-high intensity, as shown by our second systematic review (Chapter III). Hence, it is important for health care professionals to understand the potential objective and subjective barriers to practicing regular PE in order to support patients in overcoming them. Pain or discomfort, lack of willingness/interest, and work/family schedule interference negatively affect regular PE. Moreover, the recommended exercise should be as aligned with the patient's preferences as possible to prevent loss of interest and withdrawal [222].

Finally, as physiotherapists, we must be aware that some individuals with PCa consider PE unsafe for their health. Our systematic review suggested that football training should be proposed with caution: even if football training includes activities that stimulate bone osteogenesis, such as jumping, change of direction, or acceleration [276], the skill set required to play a football match could be excessive for this population. Football involves a combination of balance, muscle strength, core activity, ball skill, and attention to other players, which could be difficult for older men [277]. Despite the great adherence to this type of PE, the trials that experimented it registered several adverse events (musculoskeletal injuries), which were more frequent among those with comorbidities [278]. However, as our second systematic review showed, all those skills could be implemented safely by avoiding physical contact with others.

To summarize, the PE programs implemented for patients with PCa must be individualized, pleasant, and feasible. They must be based on the individual's needs and associated with adequate education and feedback about the benefits of adopting a healthier lifestyle. These PE programs should include moderate-high intensity activities that must be performed regularly to maintain exercise-related benefits.

Therefore, based on our systematic reviews and the descriptive study, we developed an experimental multicomponent PE intervention that combines supervised and unsupervised exercise with a step-down approach, described in Chapter V. This PE intervention is implemented in a community sports facility and is currently being tested for feasibility and safety in a small group of patients that are currently receiving ADT associated with RT. This PE intervention is aligned with individual preferences, it addresses psychophysical and cognitive functions, and it is specifically targets preventing accidental falls and fractures with an appropriate volume of exercise.

Strengths and limitations

The results of this thesis must be interpreted in light of several limitations. Firstly, in both systematic reviews, we chose to include only the RCTs which tested structured PE programs not associated with other interventions, such as nutritional and educational interventions. However, these interventions may play an important role in the prevention of accidental falls and fractures in men with PCa receiving ADT. The supplementary dietary intake of calcium and vitamin D could prevent BMD loss, while the educational counseling provided by clinicians can help patients improve their adherence to healthier behaviors [59]. It is therefore possible that PE by itself is not enough to prevent accidental falls: a combination of interventions may be more appropriate to achieve relevant goals, as suggested by the guidelines for osteoporosis [59].

Furthermore, the adherence rate to PE is provided as a cumulative index accounting for all the trials included, not for the type of exercise proposed: a low adherence rate to some types of PE could be balanced by higher rates to more pleasant activities. Thus, the estimate of PE feasibility in this population should be interpreted with caution. Moreover, the lack of any standardized way to record adverse events in the trials reviewed may have led to an incorrect estimate of the safety of these interventions.

A final consideration regards the low response rate in the cross-sectional study (51.9%), in contrast with a similar recent study on Italian cancer survivors (88.3%) [242]. This low response rate, due also to the current pandemic, does not permit any generalization of the results obtained to the whole population of men newly diagnosed with PCa.

However, a strength of this thesis is that, to date, there is no evidence to support PE as a strategy to prevent the risk of accidental falls and fractures, which are clinically relevant outcomes in this vulnerable population. The health care costs of individuals with PCa on ADT are double those of patients not treated with ADT [188]. Thus, it is necessary that further studies investigate the potential preventive role of PE on these relevant outcomes.

Furthermore, this thesis highlights the importance of educating patients about healthy lifestyles, especially at diagnosis, which appears to be a teachable moment for health care professionals to provide insights on healthier behaviors. In fact, patients who have recently been diagnosed with cancer may be more likely to change their habits if clinicians properly inform them of the potential benefits [237]. However, professionals must also motivate the patient to change by suggesting strategies to overcome the perceived barriers.

Conclusions and future perspectives

Given the beneficial effects of exercise on the healthy ageing population, PE may be a non-pharmacological strategy to reduce the risk of accidental falls and fractures in patients with cancer as well, with positive effects on health care costs and on patients' quality of life. The five-year survival rate of individuals with PCa is currently over 90% worldwide, and most of these patients experience many side effects due to treatment [5]. It is therefore time to implement evidence-based cancer rehabilitation in patients with PCa.

This thesis made it possible to develop an experimental multicomponent PE program aimed at preventing accidental falls and fractures in individuals with PCa treated with ADT and RT. The multicomponent PE intervention meets the requirements for exercise components, posology (frequency, sets, repetitions, intensity), and progression recommended by the guidelines and our systematic reviews (Chapter II and Chapter III) [41,81]. These results will inform which type of PE is required to improve adherence to the recommended exercise guidelines for cancer survivors and will help researchers plan feasible PE interventions whose effectiveness on bone health is to be verified through well-designed RCTs.

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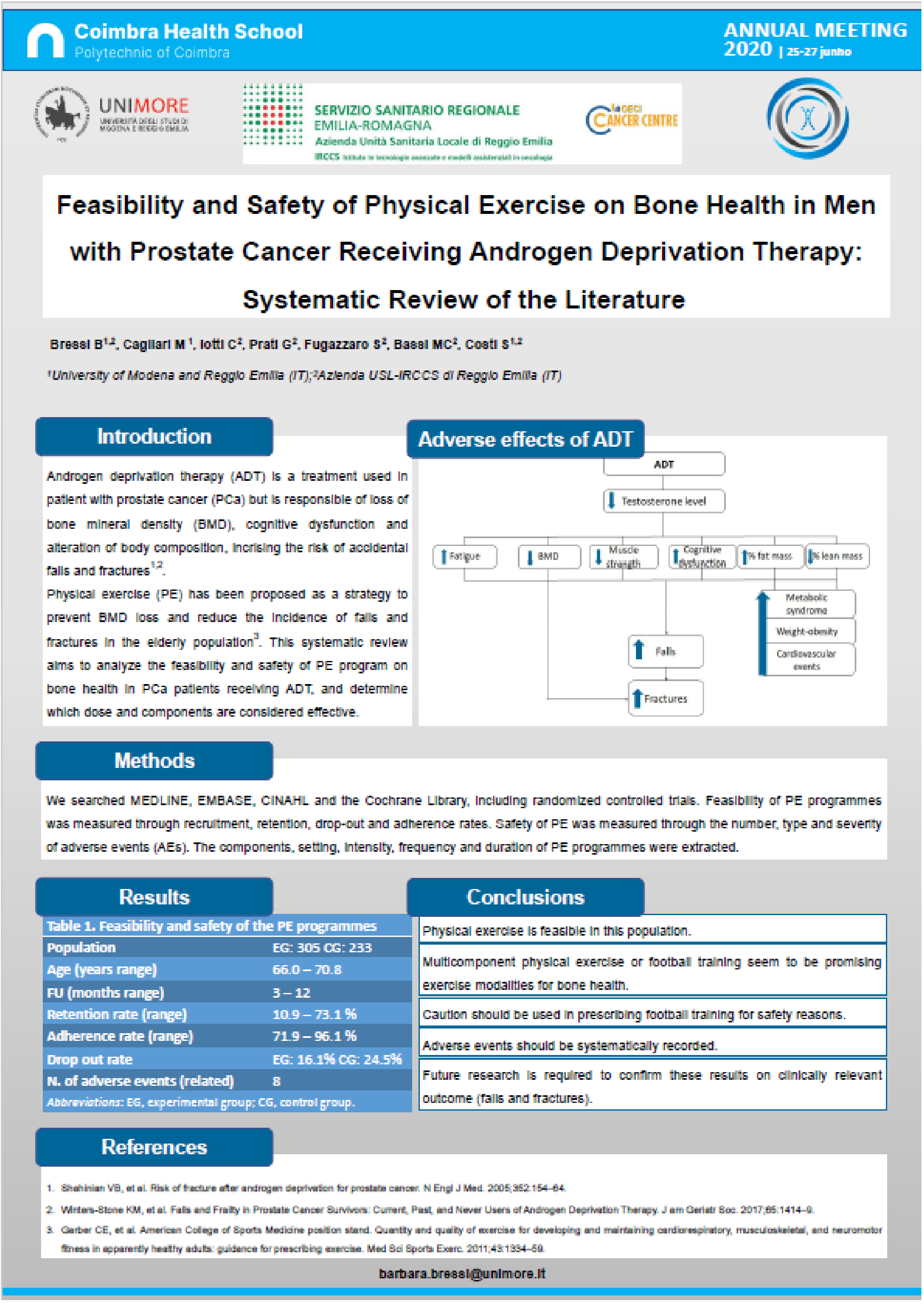
APPENDICES

Appendix I - Feasibility and safety of physical exercise on bone health in men with prostate cancer receiving androgen deprivation therapy: systematic review of the literature (poster presentation)



Coimbra Health School
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UNIMORE UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia
IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

CANCER CENTRE

Feasibility and Safety of Physical Exercise on Bone Health in Men with Prostate Cancer Receiving Androgen Deprivation Therapy: Systematic Review of the Literature

Bressi B[1,2], Cagliari M [1], Iotti C[2], Prati G[2], Fugazzaro S[2], Bassi MC[2], Costi S[1,2]

[1]University of Modena and Reggio Emilia (IT);[2]Azienda USL-IRCCS di Reggio Emilia (IT)

Introduction

Androgen deprivation therapy (ADT) is a treatment used in patient with prostate cancer (PCa) but is responsible of loss of bone mineral density (BMD), cognitive dysfunction and alteration of body composition, incrising the risk of accidental falls and fractures[1,2].

Physical exercise (PE) has been proposed as a strategy to prevent BMD loss and reduce the incidence of falls and fractures in the elderly population[3]. This systematic review aims to analyze the feasibility and safety of PE program on bone health in PCa patients receiving ADT, and determine which dose and components are considered effective.

Adverse effects of ADT

Methods

We searched MEDLINE, EMBASE, CINAHL and the Cochrane Library, including randomized controlled trials. Feasibility of PE programmes was measured through recruitment, retention, drop-out and adherence rates. Safety of PE was measured through the number, type and severity of adverse events (AEs). The components, setting, intensity, frequency and duration of PE programmes were extracted.

Results

Table 1. Feasibility and safety of the PE programmes

Population	EG: 305 CG: 233
Age (years range)	66.0 – 70.8
FU (months range)	3 – 12
Retention rate (range)	10.9 – 73.1 %
Adherence rate (range)	71.9 – 96.1 %
Drop out rate	EG: 16.1% CG: 24.5%
N. of adverse events (related)	8

Abbreviations: EG, experimental group; CG, control group.

Conclusions

Physical exercise is feasible in this population.

Multicomponent physical exercise or football training seem to be promising exercise modalities for bone health.

Caution should be used in prescribing football training for safety reasons.

Adverse events should be systematically recorded.

Future research is required to confirm these results on clinically relevant outcome (falls and fractures).

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3. Garber CE, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43:1334–59.

barbara.bressi@unimore.it

Appendix II - Esercizio fisico per la salute. Guida al programma di esercizio fisico per pazienti con carcinoma prostatico sottoposti a ormonoterapia e radioterapia (public engagement)

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia
IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

ESERCIZIO FISICO PER LA SALUTE

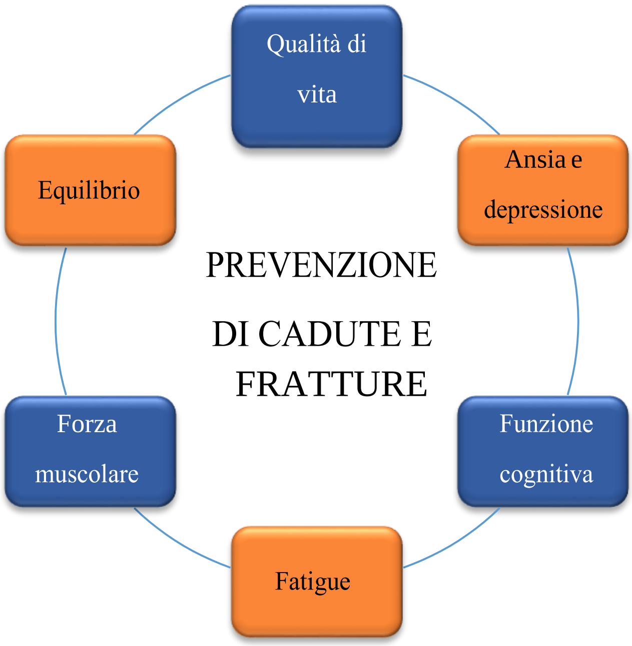
Guida al programma di esercizio fisico per pazienti con carcinoma prostatico sottoposti a ormonoterapia e radioterapia

FONDAZIONE
CASSA DI RISPARMIO
DI REGGIO EMILIA
PIETRO MANODORI

INDICE

PRESENTAZIONE

Questo opuscolo è nato per supportare i pazienti che partecipano al progetto di ricerca "Fattibilità e sicurezza di un programma di esercizio fisico nei pazienti con tumore alla prostata che ricevono terapia di deprivazione androgenica e radioterapia".
Il progetto nasce dalla collaborazione tra la Medicina Fisica e Riabilitativa e la Radioterapia dell'Azienda USL-IRCCS di Reggio Emilia. L'obiettivo è quello di verificare la fattibilità, la sicurezza e illivello di gradimento di un programma di esercizio fisico volto, in modo particolare, alla prevenzione degli eventi di cadute e fratture attraverso il miglioramento dei seguenti parametri e sintomi.



Questo opuscolo è stato pensato per esserle di supporto nella partecipazione alle sedute di esercizio fisico previste dal programma, in particolare durante il periodo in cui le sedute saranno svolte senza supervisione da parte del Fisioterapista. Inoltre, fornisce una traccia che potrà essere d'aiuto in qualsiasi altro momento del percorso di cura.

Le informazioni contenute in questo opuscolo non intendonosostituire il colloquio diretto con i professionisti sanitari. Usi questo opuscolo come spunto per domande e richieste.

INTRODUZIONE

QUALI SONO I BENEFICI DELL'ATTIVITA' FISICA

Secondo l'Organizzazione Mondiale della Sanità (OMS), l'adozionedi uno stile di vita salutare, che comprende una regolare attività fisica, ha un effetto benefico sulla qualità della vita a ogni età. L'attività fisica, infatti, agisce positivamente sia sullo stato di salute (prevenendo e/o alleviando molte patologie croniche) sia sulbenessere psichico e sociale. L'attività fisica aiuta a prevenire le malattie metaboliche (diabete, dislipidemie), cardiovascolari (ipertensione, coronaropatie, ictus) e tumorali (riduzione del rischio di alcuni tipi di tumori); è importante per controllare il peso corporeo e ridurre il grasso in eccesso apportando benefici all'intero organismo.
Intraprendere regolarmente un programma di attività fisica aiuta a mantenere in salute muscoli e ossa, e a prevenire artrosi, osteoporosi, fratture e cadute. Infine, l'attività fisica contribuisce anche a ridurre il rischio di depressione, ansia, stress e solitudine.

QUALE TIPO DI ATTIVITA' FISICA POSSO FARE?

Secondo l'Organizzazione mondiale della sanità, per "attività fisica" s'intende "qualunque movimento del corpo che produce un dispendio energetico superiore a quello delle condizioni di riposo". Con questa definizione si fa riferimento non solo alla semplice attività sportiva, ma anche a tutti quei movimenti svolti durante il corso della giornata come camminare, andare in bicicletta, ballare, giocare, fare giardinaggio e lavori domestici.
L'attività fisica svolta in forma quantificata, pianificata ed eseguitaregolarmente viene indicata con il termine di "esercizio fisico".

QUANTO ESERCIZIO FISICO DEVO FARE PER OTTENERE I BENEFICI PER LA SALUTE?

5 VOLTE A SETTIMANA	2-3 VOLTE A SETTIMANA
ESERCIZIO AEROBICO	ESERCIZI DI RINFORZO
nuotare, camminare, correre, andare in bicicletta, attività sportive	forza, equilibrio, coordinazione, flessibilità
Almeno 30 minuti a seduta a moderata	Almeno 30 minuti a moderata-elevata intensità

Va evidenziato comunque che non esiste una soglia sotto la quale ilmovimento non produca effetti positivi per la salute. Il passaggio,quindi, dalla sedentarietà a un livello di attività anche inferiore rispetto a quello considerato sufficiente dalle linee guida rappresenta un risultato importante (*American College of Sports Medicine, 2010*).

PER QUANTO TEMPO DEVO FARE ESERCIZIO FISICO?

Per mantenere nel tempo gli effetti benefici, l'esercizio fisico deve essere svolto con regolarità e costanza, trasformandosi in una vera e propria abitudine.
Per questo non è consigliabile agire seguendo la regola del "tutto e subito" o di "una volta ogni tanto", con sessioni intense per un limitato periodo di tempo o sessioni molto diradate.
Risulta fondamentale cercare di cambiare il proprio stile di vita, rendendo così l'esercizio fisico una vera e propria abitudine. Questo rende l'esercizio fisico uno strumento valido per raggiungere obiettivi di salute.

IL NOSTRO PROGRAMMA DI ESERCIZIO FISICO

Le proponiamo di seguito un programma di esercizio fisico diviso intre sezioni:

- Esercizi aerobici
- Esercizi di rinforzo muscolare
- Esercizi di equilibrio, coordinazione e salto

Lo scopo del programma è apportare beneficio alla sua salute,lavorando per:

- ✓ Rinforzare ossa e muscoli (apparato muscolo-scheletrico)
- ✓ Migliorare memoria, attenzione, coordinazione, equilibrio (funzioni cognitive)
- ✓ Controllare il peso corporeo, migliorare la composizione corporea (metabolismo)
- ✓ Migliorare l'efficienza del sistema cardiocircolatorio (apparato cardiovascolare)

Legenda dei simboli


Durata dell'esercizio. L'orologio indica il tempo di allenamento per ogni singolo esercizio.


Ripetizioni. La freccia rossa indica il numero di movimenti completi previsti per l'esercizio e il numero di serie, ossia le ripetizioni da eseguire dopo un breve intervallo. Le consigliamo 2 minuti di riposo tra una serie e l'altra.
Ad esempio, se l'esercizio prevede di alzare il braccio e il simbolo indica 10 ripetizioni per 2 serie, significa che dovrò alzare il bracciodieci volte (prima serie), poi riposarmi per due minuti e rialzare il braccio per altre dieci volte (seconda serie).

Varianti. Con questo simbolo vengono indicati degli esercizi alternativi a quello proposto che presentano minore o maggiore difficoltà oppure varianti che prevedono l'utilizzo di attrezzi diversi

INIZIAMO IMPARANDO A RESPIRARE

La respirazione è composta da due fasi:

Inspirazione: dal naso si riempiono i polmoni d'aria, ricca di ossigeno.

Espirazione: dalla bocca si svuotano i polmoni e si espelle anidridecarbonica.

Questa fase dovrebbe durare circa il doppio dell'inspirazione.

Sdraiarsi con le ginocchia piegate e mettere una mano sulla pancia a livello dell'ombelico. Mentre si inspira aria dal naso, gonfiare la pancia rimanendo rilassato. Quindi espirare lentamente a labbra socchiuse sgonfiando la pancia.

Mantenere questa respirazione per 3-4 minuti è utile come attività di recupero tra un esercizio e l'altro.

ESERCIZI AERBOCI

Di seguito vengono proposti una serie di esercizi che possono essere svolti liberamente in base alle sue preferenze:

- Camminare
- Correre
- Cyclette/bicicletta
- Attività sportive
  - ballo,
  - tennis,
  - pallavolo,
  - basket,
  - etc.

20-30 minuti a moderata intensità

COME RICONOSCERE CHE CI SI STA ALLENANDO A MODERATA INTENSITA'?

Recenti studi hanno dimostrato l'efficacia del "talk test".

Con questo semplice metodo le si chiede di parlare durantel'esecuzione dell'esercizio (es. corsa).

Se le è possibile parlare in modo confortevole o addirittura canticchiare allora si sta allenando con una leggera (molto leggera) intensità.

Se le è possibile parlare con qualche difficoltà, l'intensità è moderata. Questo è il tipo di allenamento richiesto.

Se le è possibile pronunciare solo frasi molto brevi o addirittura è quasi impossibile parlare allora si sta allenando ad una intensità vigorosa (molto intensa).

ESERCIZI DI RINFORZO MUSCOLARE

STEP SU RIALZO

Mettere un piede su un rialzo, un gradino o uno step. Stendere la gamba e salire sul gradino. Ritornare lentamente alla posizione di partenza.

8-15 ripetizioni per gamba, 2-4 serie

PONTE

Sdraiarsi a pancia in su con i piedi in appoggio a terra, aperti alla larghezza del bacino. Tenete le braccia lungo il corpo leggermente aperte con i palmi delle mani appoggiati a terra. Mentre si inspira sollevare il bacino a contrarre i glutei (attenzione a mantenere la schiena sempre nella stessa posizione durante il movimento). Mentre si espira, scendere lentamente e tornare alla posizione di partenza.

> Proposta con attrezzo. Eseguire l'esercizio con i piedi in appoggio su una palla fitball o tenere una palla o un cuscino tra le ginocchia per aumentare la contrazione dei muscoli della coscia.






8-15 ripetizioni, 2-4 serie

TORSIONI DEL TRONCO E DISTENSIONI ARTI SUPERIORI

In piedi con un peso in mano di 2-3 Kg. Tenere le gambe leggermente divaricate, senza superare la larghezza del bacino. Ruotare il tronco lateralmente e distendere le braccia. Ripetere prima da un lato e poi dall'altro.

Se non si possiede un peso come in foto, si può utilizzare un oggetto dal peso di 2 Kg (es. bottiglia d'acqua da 2 litri piena).

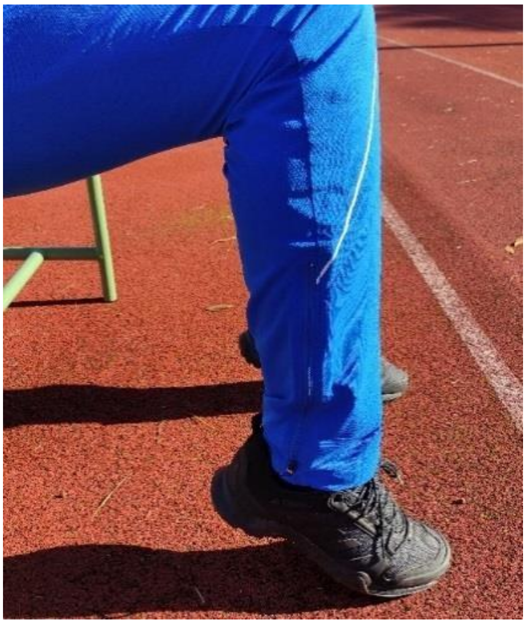
8-15 ripetizioni per lato, 2-4 serie

SPINTE SUI PIEDI

Alzarsi sulle punte dei piedi e scendere lentamente. Le prime volte eseguire l’esercizio appoggiato ad un muro o a un tavolo, oppure da seduto.

8-15 ripetizioni, 2-4 serie





ESTENSIONI DELLA GAMBA DA SEDUTO

Stendere un ginocchio per volta e mantenere la posizione per almeno 5 secondi. Si può stringere una palla o un cuscino tra le ginocchia per aumentare la contrazione dei muscoli della coscia.

8-15 ripetizioni per lato, 2-4 serie

SQUAT AL MURO

Posizionarsi in appoggio al muro con la schiena e le ginocchia piegate. Mantenere la posizione per almeno 10 secondi. Si può stringere una palla o un cuscino tra le ginocchia per aumentare lacontrazione dei muscoli della coscia.

20-60 secondi, 2-4 serie

SPINTE CON ELASTICO

Dalla posizione seduta mettere l’elastico sotto la pianta del piede etirarlo verso di sé. Spingere verso il basso la punta del piede, mantenendo la posizione per 5 secondi e poi tornare lentamente alla posizione iniziale.

Mettere l’elastico a livello della caviglia. Tenere la gamba distesa e avvicinare il piede all’altra gamba, in chiusura.
Rilasciare lentamente.

8-15 ripetizioni, 2-4 serie

Mettere l’elastico intorno alle ginocchia piegate. Aprire le ginocchiain fuori e poi rilasciare lentamente.

IN PIEDI DISTENSIONI DEL BRACCIO IN AVANTI E LATERALMENTE

Mettere l’elastico attorno ad un supporto per fissarlo (es. spalliera o maniglia della porta). Partire con il braccio steso davanti a sé. Portare il braccio indietro e verso il basso tirando l’elastico fino al bacino. Ritornare lentamente alla posizione di partenza.

Iniziare con il braccio staccato dal corpo lateralmente. Mantenendo il gomito steso avvicinare il braccio al corpo e rilasciare lentamente.

8-15 ripetizioni, 2-4 serie

IN PIEDI ROTAZIONI ESTERNA E INTERNA DEL BRACCIO

Piegare il gomito a 90° vicino al corpo. Tirare l’elastico verso l’esterno mantenendo il gomito vicino al corpo. Rilasciare lentamente.

Piegare il gomito a 90° vicino al corpo. Tirare l’elastico verso l’interno mantenendo il gomito vicino al corpo. Rilasciare lentamente.

8-15 ripetizioni, 2-4 serie

ESERCIZI A CORPO LIBERO O CON I PESI

In piedi o da seduto unire le mani e tenere i gomiti distesi. Portare le braccia verso l'alto sopra la testa. Le spalle non devono avvicinarsi alle orecchie ma occorre tenerle abbassate.

In piedi o da seduti mantenere le braccia lungo i fianchi e i gomitidistesi. Aprire le braccia lateralmente fino all'altezza delle spalle eritornare lentamente alla posizione di partenza.

8-15 ripetizioni, 2-4 serie

ESERCIZI DI EQUILIBRIO, COORDINAZIONE E SALTO

SALTO A PIEDI PARI

Dalla posizione eretta, aiutandosi con le braccia, piegare le ginocchia e fare un balzo in avanti atterrando a piedi pari (partenza e atterraggio a piedi uniti). Eseguire dei saltelli piedi pari sul posto con o senza corda.



START E STOP

Fare tre passi camminando. Quando si esegue l'ultimo passo, fermarsi in appoggio su un solo piede mentre si alza l'altra gambatenendo il ginocchio piegato. Mantenere la posizione per cinque secondi per poi riprendere a camminare.



8-15 ripetizioni, 2-4 serie

PERCORSO AD OSTACOLI

Camminare o correre tra ostacoli bassi, cerchi e coni segnalatori. Gli ostacoli posizionati possono essere superati o aggirati (slalom), osaltati con due piedi uniti o con un solo piede.
Posizionare gli ostacoli in successione alla distanza circa di 1 metro uno dall'altro. Se possibile utilizzare almeno cinque ostacoli per creare una sequenza.
Se non si hanno ostacoli bassi, cerchi o coni segnalatori, è possibileutilizzare anche ostacoli come sedie o bottiglie.



8-15 ripetizioni,
2-4 serie

Proposta senza attrezzi. Nel primo periodo in cui si prende confidenza con l'esercizio, o anche successivamente, se non si ha disponibilità di materiale, si può scegliere di eseguire l'esercizio camminando o correndo lungo un percorso immaginario con andatura a zig-zag o a slalom senza l'utilizzo di oggetti.

EQUILIBRIO

Gli esercizi di equilibrio possono essere effettuati in posizione eretta in appoggio con due piedi o con un piede solo, ad occhi aperti o ad occhi chiusi. Di seguito viene proposto un esercizio di equilibrio con le sue possibili progressioni in ordine di difficoltà (dal più semplice al più complesso):

- Stare in equilibrio con un piede davanti all’altro. Ripetere l’esercizio cambiando la gamba che sta davanti.
- Stare in equilibrio su un piede solo con braccia aperte ad altezza delle spalle come a formare la lettera “T”.
- Stare in equilibrio su un piede solo con braccia lungo i fianchi.
- Stare in equilibrio su una pedana instabile (foto) con entrambi i piedi, braccia allargate a T.

20-60 secondi, 2-4 serie

Per sicurezza, eseguire tutti questi esercizi di equilibrio vicino ad un supporto (muro o tavolo) in modo d’avere una solida base d’appoggio. Solo quando l’esercizio viene eseguito senza difficoltà, iniziare a staccare per qualche secondo la mano in appoggio cercando di mantenere l’equilibrio, aumentando progressivamente il tempo senza appoggio. Come ultimo step eseguire gli esercizi ad occhi chiusi.

EQUILIBRIO ESECUZIONE DI UN COMPITO

Stare in equilibrio sulla pedana con entrambi i piedi o con un solo piede mentre si distendono in avanti le braccia o mentre si lancia una palla.

8-15 ripetizioni, 2-4 serie


DISCESA DAL GRADINO

Scendere da un gradino di circa 20 cm camminando o con un piccolo balzello.


8-15 ripetizioni, 2-4 serie

CAMMINO O CORSA IN SALITA E DISCESA

- Salire e scendere le scale in camminata o corsa.

- Camminare o correre su terreno in salita e in leggera discesa




5-10 minuti, 2-4 serie

ESERCIZI DI FLESSIBILITA'/ STRETCHING

Normalmente gli esercizi di stretching servono ad allungare i muscoli e a migliorare la mobilità delle articolazioni. Perché siano efficaci occorre mantenere le posizioni almeno **20-30 secondi** per fare in modo che i muscoli si adattino all'allungamento. Questi esercizi vanno eseguiti **lentamente e dolcemente** e sono maggiormente consigliati alla fine della seduta di esercizio fisico. Questo perché imuscoli **"caldi"** sono più plastici per cui facilmente allungabili. Di seguito vengono illustrati alcuni esercizi di stretching con cui terminare la seduta di esercizio fisico.

DIARIO SETTIMANALE

Questa sezione permette di registrare con cadenza giornaliera la modalità e la durata dell'esercizio fisico praticato.

Questa scheda rappresenta la traccia per un piano settimanale. Può stamparne più copie per monitorare la frequenza con cui esegue l'esercizio fisico.

Per ogni giorno indichi con una X quale tipo di esercizio ha fatto (esercizio aerobico, esercizi di rinforzo, esercizi di equilibrio- coordinazione-salto) e scriva il tempo di allenamento fatto per ogni sezione.

Es. Se lunedì pratica 20 minuti di corsa (esercizio aerobico) e 10 minuti di esercizi per l'equilibrio-coordinazione e salto, dovrà segnare come di seguito:

Data	Esercizi aerobici		Esercizi dirinforzo muscolare		Esercizi di equilibrio, coordinazione esalto	
LUNEDÌ 04/01/2021	X	Tempo 20 minuti		Tempo _____ min	X	Tempo 10 minuti

LA MIA SETTIMANA

	Esercizi aerobici		Esercizi di rinforzo muscolare		Esercizi di equilibrio, coordinazione e salto	
LUNEDÌ __/__/______		Tempo ____ Min		Tempo ____ Min		Tempo ____ Min
MARTEDÌ __/__/________		Tempo ____ Min		Tempo ____ Min		Tempo ____ Min
MERCOLEDÌ __/__/_______		Tempo ____ Min		Tempo ____ Min		Tempo ____ Min
GIOVEDÌ __/__/________		Tempo ____ Min		Tempo ____ Min		Tempo ____ Min
VENERDÌ __/__/________		Tempo ____ Min		Tempo ____ Min		Tempo ____ Min
SABATO __/__/________		Tempo ____ Min		Tempo ____ Min		Tempo ____ Min
DOMENICA __/__/_______		Tempo ____ Min		Tempo ____ Min		Tempo ____ Min

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TESTI A CURA DI

Barbara Bressi, Fisioterapista, Dipartimento Neuromotorio e Riabilitativo, S.C di Medicina Fisica e Riabilitativa, Azienda USL - IRCCS di Reggio Emilia.

Maribel Cagliari, Studentessa del CdL in Fisioterapia, DipartimentoChirurgico, Medico, Odontoiatrico e di Scienze Morfologiche con interesse Trapiantologico, Oncologico e di Medicina Rigenerativa, Università di Modena e Reggio Emilia.

REVISIONE A CURA DI

Stefania Costi, Fisioterapista Ricercatore, Direzione Scientifica,Azienda USL - IRCCS di Reggio Emilia. Dipartimento Chirurgico, Medico, Odontoiatrico e di Scienze Morfologiche con interesse Trapiantologico, Oncologico e di Medicina Rigenerativa, Universitàdegli studi di Modena e Reggio Emilia.

Stefania Fugazzaro, Medico fisiatra, Dipartimento Neuromotorio eRiabilitativo, S.C di Medicina Fisica e Riabilitativa, Azienda USL - IRCCS di Reggio Emilia.

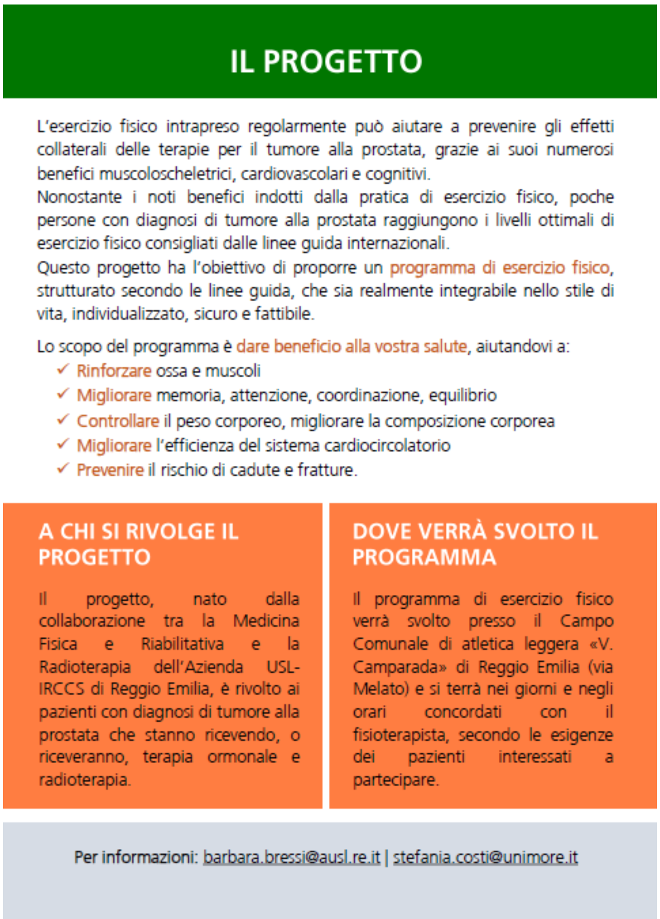
FOTO A CURA DI

Si ringrazia il Gruppo Sportivo Self Atletica Montanari & Gruzza ASD di Reggio Emilia per aver partecipato all'esecuzione degli esercizi che hanno permesso la realizzazione delle fotografie illustrate in questo opuscolo.

Ultimo aggiornamento: febbraio 2021

NOTE

Appendix III - Tumore alla prostata: i vantaggi dell'esercizio fisico (public engagement)



IL PROGETTO

L'esercizio fisico intrapreso regolarmente può aiutare a prevenire gli effetti collaterali delle terapie per il tumore alla prostata, grazie ai suoi numerosi benefici muscoloscheletrici, cardiovascolari e cognitivi.
Nonostante i noti benefici indotti dalla pratica di esercizio fisico, poche persone con diagnosi di tumore alla prostata raggiungono i livelli ottimali di esercizio fisico consigliati dalle linee guida internazionali.
Questo progetto ha l'obiettivo di proporre un programma di esercizio fisico, strutturato secondo le linee guida, che sia realmente integrabile nello stile di vita, individualizzato, sicuro e fattibile.

Lo scopo del programma è dare beneficio alla vostra salute, aiutandovi a:
- ✓ Rinforzare ossa e muscoli
- ✓ Migliorare memoria, attenzione, coordinazione, equilibrio
- ✓ Controllare il peso corporeo, migliorare la composizione corporea
- ✓ Migliorare l'efficienza del sistema cardiocircolatorio
- ✓ Prevenire il rischio di cadute e fratture.

A CHI SI RIVOLGE IL PROGETTO

Il progetto, nato dalla collaborazione tra la Medicina Fisica e Riabilitativa e la Radioterapia dell'Azienda USL-IRCCS di Reggio Emilia, è rivolto ai pazienti con diagnosi di tumore alla prostata che stanno ricevendo, o riceveranno, terapia ormonale e radioterapia.

DOVE VERRÀ SVOLTO IL PROGRAMMA

Il programma di esercizio fisico verrà svolto presso il Campo Comunale di atletica leggera «V. Camparada» di Reggio Emilia (via Melato) e si terrà nei giorni e negli orari concordati con il fisioterapista, secondo le esigenze dei pazienti interessati a partecipare.

Per informazioni: barbara.bressi@ausl.re.it | stefania.costi@unimore.it

Appendix IV - Physical exercise and lifestyle behaviours among men with prostate cancer: a cross sectional study (poster presentation)

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia

UNIMORE

PRESENTED AT:
World Physiotherapy Congress2021 online

Physical exercise and lifestyle behaviours among men with prostate cancer: a cross sectional study

BRESSI B[1,2], IOTTI C[2], CAGLIARI M[3], STEFANIA FUGAZZARO[2], BERGAMASCHI FAM[2], MOSCATO A[2], CAVUTO S[2], COSTI S[2,3]

[1]PhD Program in Clinical and Experimental Medicine, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Italy
[2]Azienda USL–IRCCS di Reggio Emilia, Italy
[3]Department of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy

Introduction

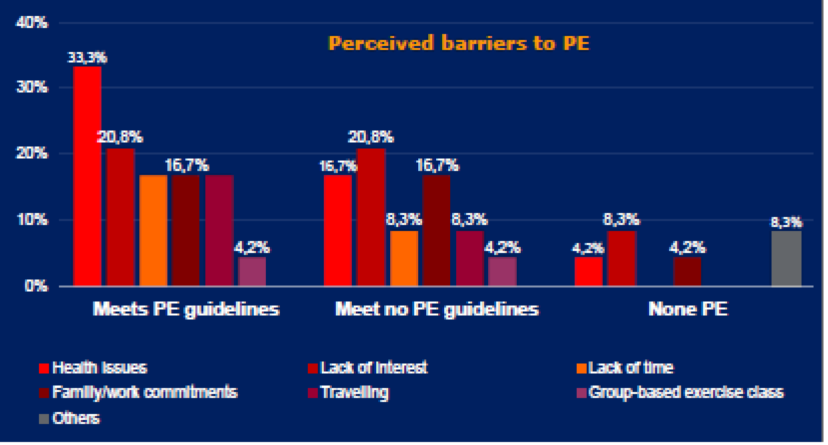
Quality of life of patients with prostate cancer (PCa) is negatively affected by side effects of curative treatments. Physical exercise (PE) is recommended to improve clinical and functional outcomes in this population and should be becoming a healthy habit[1]. However, only 41.9% of men with PCa perform the recommended amount of PE[2]. Hence, a deep understanding of patient motivation and perceived barriers to exercise seems fundamental to promote feasible PE interventions and the adherence to a healthier lifestyle.

Methods

Italian men with newly diagnosis of PCa were invited to participate in an interview.
We collected data on the patients' PE, smoking, eating, and drinking daily habits.
We also investigated the perceived impact of lifestyle on patients' health and barriers to a potential change towards healthier habits

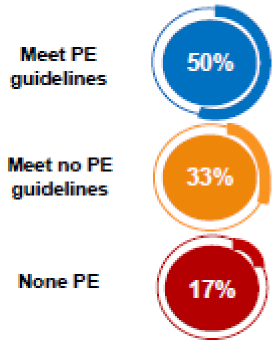
Conclusions and implications

Preliminary results show the half of patients with PCa do not reach the desirable levels of physical exercise
Feasible and acceptable exercise programme need to take in consideration patient preferences
Physiotherapists should apply approaches to foster health promotion in patients with PCa



Results

Almost all twenty-four participants were not willing to change their eating and drinking habits, although 46% declare themselves aware of being overweight and of the appropriateness to improve them.



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barbara.bressi@unimore.it

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