Exercise and Cancer Survivorship

Impact on Health Outcomes and Quality of Life
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Impact on Health Outcomes and Quality of Life
Foreword

The volume of evidence for the health benefits of PA has grown exponentially in the last 20 years (Department of Health, 2004; United States Department of Health and Human Services, 2008). These benefits include reduced risk of a range of diseases, including CV disease, obesity, diabetes and mental conditions such as dementia and depression. Increasingly, PA is also indicating its effectiveness in therapy.

The role of PA in the prevention and treatment of cancers has only recently come to the forefront. The WCRF Report (2007) clearly established that PA reduces the risk of a range of cancers, with the evidence for the prevention of colon and breast cancer being most convincing. Less public health attention has been paid to the worth of PA in therapy and recovery from cancer.

PA has lots of potential in this setting. There are intuitive and plausible biomedical mechanisms by which exercise might improve prognosis for survival. Additionally, the many established psychological benefits that exercise is able to bring may be particularly potent for cancer recoverers. It has the potential to energise, improve physical function and mood and its positive action may bring hope and optimism to an otherwise difficult challenge. A steady stream of studies and systematic reviews is indicating that these benefits can be realised and a comprehensive exposition of key issues is now overdue.

John Saxton and Amanda Daley, through this book, have achieved just this. Both have been heavily involved in research in PA as therapy for cancer for over a decade. They have drawn upon their experiences to identify cogent topics around the evidence and potential for PA in cancer recovery. To help them in this mission they have engaged experts from leading teams from around the world who have applied their experiences to a research or practical question. The result is a volume that provides fascinating insight into the complexities that make up this area of work. Different effects are likely for different cancers. Exercise dose response may be different for outcomes that can be as diverse as improved chance of survival to better QoL. Then, as always, there is the matter of creating conditions that will engage the patients themselves and facilitate their success. Above all, this book has brought to light the
importance of PA as a therapeutic medium for cancer and established the need for more investment in systematic and sequential research. Enjoy.

University of Bristol
June 2009
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Contributors

Shabbir M.H. Alibhai  Division of Clinical Decision Making and Healthcare, Toronto General Research Institute, Toronto General Hospital, Ontario, Canada M5G 2C4, shabbier.alibhai@uhn.on.ca

William J. Aronson  Department of Urology, David Geffen School of Medicine, University of California, Los Angeles, CA 90095-1606, USA, waronson@ucla.edu

R. James Barnard  Department of Physiological Science, David Geffen School of Medicine, University of California, Los Angeles, CA 90095-1606, USA, jbarnard@physci.ucla.edu

N. Tim Cable  Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK, t.cable@ljmu.ac.uk

Kerry S. Courneya  Department of Physical Therapy, University of Alberta; Department of Oncology, Cross Cancer Institute, Edmonton, AB T6G 1Z2, Canada, kerry.courneya@ualberta.ca

Helen Crank  Faculty of Health and Wellbeing, Centre for Sport and Exercise Science, Sheffield Hallam University, Sheffield, S10 2BP, UK, h.crank@shu.ac.uk

N. Culos-Reed  Department of Kinesiology, Dalhousie University, Halifax, Nova Scotia, Canada, nculosre@ucalgary.ca

Amanda Daley  Primary Care Clinical Sciences, School of Health and Population Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK, a.daley@bham.ac.uk

Keith George  Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK

Najib Haboubi  Department of Pathology, Trafford General Hospital NHS Trust, Manchester, UK, najibhaboubi@hotmail.com

David J. Harriss  Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK, d.harriss@ljmu.ac.uk
Michelle Harvie  University Hospital South Manchester, Manchester, M23 9LT, UK, michelle.harvie@manchester.ac.uk

Monique M. Hochstenbag  Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands, m.hochstenbag@mumc.nl

Melinda L. Irwin  Epidemiology and Public Health, Yale School of Public Health, New Haven, CT 06520-8034, USA, melinda.irwin@yale.edu

Lee W. Jones  Duke University Medical Center, Durham, North Carolina, NC 27710, USA, lee.w.jones@duke.edu

Khaled Mansour  Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands, k.mansour@sjgweert.nl

Martina Markes  German Institute for Health Research gGmbH, D-08645 Bad Elster, Germany, martina.markes@googlemail.com

Margaret L. McNeely  Department of Physical Therapy, University of Alberta; Department of Oncology, Cross Cancer Institute, Edmonton, AB T6G 1Z2, Canada, mmcneely@ualberta.ca

Thomas Reilly  Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK

Andrew G. Renehan  Department of Surgery, Christie Hospital NHS Trust, Manchester, UK, andrew.renehan@btinternet.com

Paul Ritvo  Population Studies and Surveillance, Cancer Care Ontario, University Avenue, Toronto, Ontario, Canada M5G 2L7, paul.ritvo@cancercare.on.ca

Daniel Santa Mina  Department of Surgical Oncology, University Health Network, Toronto, Ontario, Canada, dstamina@gmail.com

John Saxton  School of Allied Health Professions, Faculty of Health, Queen’s Building, University of East Anglia, Norwich, NR4 7TJ, UK, john.saxton@uea.ac.uk

Roanne Segal  Ottawa Hospital Regional Cancer Center, University of Ottawa Heart Institute, Ottawa, Ontario, Canada, rsegal@ottawahospital.on.ca

Martijn A. Spruit  Department of Research, Development and Education of the Centre for Integrated Rehabilitation of Organ failure (CIRO), Horn, The Netherlands, martijnspruit@proteion.nl

Clare Stevinson  Macmillan Research Unit, School of Nursing, Midwifery, and Social Work, University of Manchester, Manchester, M13 9PL, UK, clare.stevinson@manchester.ac.uk
Emiel F.M. Wouters  Department of Research, Development and Education of the Centre for Integrated Rehabilitation of Organ failure (CIRO), Horn, The Netherlands; Department of Respiratory Medicine of the Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands, e.wouters@mumc.nl
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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACS</td>
<td>American Cancer Society</td>
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<tr>
<td>ADT</td>
<td>Androgen deprivation therapy</td>
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<td>AICR</td>
<td>American Institute for Cancer Research</td>
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<tr>
<td>AS</td>
<td>Active surveillance</td>
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<tr>
<td>AT</td>
<td>Anaerobic threshold</td>
</tr>
<tr>
<td>ATAC</td>
<td>Arimidex or Tamoxifen alone or in combination</td>
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<tr>
<td>BCN</td>
<td>Breast care nurse</td>
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<tr>
<td>BFI</td>
<td>Brief fatigue inventory</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
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<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BPH</td>
<td>Benign prostatic hyperplasia</td>
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<tr>
<td>BT</td>
<td>Brachytherapy</td>
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<tr>
<td>CALGB</td>
<td>Cancer and leukemia group B</td>
</tr>
<tr>
<td>C-CLEAR</td>
<td>Colorectal cancer, lifestyle, exercise and research</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence intervals</td>
</tr>
<tr>
<td>CMF</td>
<td>Cyclophosphamide, methotrexate, fluorouracil</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated standards of reporting trials</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CPET</td>
<td>Cardiopulmonary exercise test</td>
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<tr>
<td>CRF</td>
<td>Cancer-related fatigue</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>CRUK</td>
<td>Cancer Research UK</td>
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<td>CT</td>
<td>Computerised tomography</td>
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<td>CV</td>
<td>Cardiovascular</td>
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<tr>
<td>CWLS</td>
<td>Collaborative women’s longevity study</td>
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<tr>
<td>DEXA or DXA</td>
<td>Dual energy x-ray absorptiometry</td>
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<td>DRE</td>
<td>Digital rectal examinations</td>
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<td>EBR</td>
<td>External beam radiation</td>
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<td>EM</td>
<td>Expectant management</td>
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<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
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<tr>
<td>ES</td>
<td>Effect size</td>
</tr>
<tr>
<td>FACT-C</td>
<td>Functional assessment of cancer therapy – colorectal</td>
</tr>
<tr>
<td>FACT-F</td>
<td>Functional assessment of cancer therapy – fatigue scale</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>FACT-G</td>
<td>Functional assessment of cancer therapy – general</td>
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<tr>
<td>FACT-L</td>
<td>Functional assessment of cancer therapy – lung</td>
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<tr>
<td>FACT-P</td>
<td>Functional assessment of cancer therapy – prostate</td>
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<tr>
<td>FBS</td>
<td>Fetal bovine serum</td>
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<tr>
<td>FEC</td>
<td>Fluorouracil, epirubicin, cyclophosphamide</td>
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<tr>
<td>FFM</td>
<td>Fat-free mass</td>
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<tr>
<td>FQ</td>
<td>Fatigue questionnaire</td>
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<td>GTT</td>
<td>Gastrointestinal transit-time</td>
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<tr>
<td>Hb</td>
<td>Hemoglobin</td>
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<tr>
<td>HEAL</td>
<td>Health, eating, activity and lifestyle</td>
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<tr>
<td>HIF</td>
<td>Hypoxia-inducible factor</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>HSCT</td>
<td>Hematopoietic stem cell transplantation</td>
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<td>IGF</td>
<td>Insulin-like growth factor</td>
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<td>IGFBP</td>
<td>Insulin-like growth factor binding protein</td>
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<tr>
<td>IL-1ra</td>
<td>Interleukin-1 receptor antagonist</td>
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<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
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<tr>
<td>Ki-ras</td>
<td>Kirsten-ras</td>
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<tr>
<td>LEAD</td>
<td>Leading the way in exercise and diet</td>
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<tr>
<td>LNCaP</td>
<td>Lymph node-derived PCA cell proliferation</td>
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<tr>
<td>MAPK</td>
<td>Mitogen-activated protein kinase</td>
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<tr>
<td>MCCS</td>
<td>Melbourne collaborative cohort study</td>
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<tr>
<td>MET</td>
<td>Metabolic equivalent task</td>
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<tr>
<td>MFI</td>
<td>Multi-dimensional fatigue inventory</td>
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<tr>
<td>MFSI</td>
<td>Multi-dimensional fatigue symptom inventory</td>
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<td>MHR</td>
<td>Maximum heart rate</td>
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<td>MMPs</td>
<td>Matrix metalloproteases</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
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<tr>
<td>NIDDM</td>
<td>Non insulin-dependent diabetes mellitus</td>
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<td>NIHR</td>
<td>National Institute for Health Research</td>
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<tr>
<td>NMES</td>
<td>Neuromuscular electrical stimulation</td>
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<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<td>NSCLC</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PA</td>
<td>Physical activity</td>
</tr>
<tr>
<td>PCa</td>
<td>Prostate cancer</td>
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<tr>
<td>PCNA</td>
<td>Proliferating cell nuclear antigen</td>
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<tr>
<td>PFS</td>
<td>Piper fatigue scale</td>
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<tr>
<td>PI-3 K</td>
<td>Phosphatidylinositol 3-kinase</td>
</tr>
<tr>
<td>POSH</td>
<td>Prospective study of outcomes in sporadic versus hereditary breast cancer</td>
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<tr>
<td>PSA</td>
<td>Prostate-specific antigen</td>
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<tr>
<td>QoL</td>
<td>Quality of life</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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</table>
List of Abbreviations

REE  Resting energy expenditure
RER  Respiratory exchange ratio
RP   Radical prostatectomy
RPE  Rate of perceived exertion
RR   Relative risk
RT   Radiotherapy
SCFS Schwartz cancer fatigue scale
SCLC Small cell lung cancer
SEER Surveillance epidemiology and end results
SHERBERT Sheffield exercise and breast randomised trial
SMD  Standardized mean difference (effect size)
TLR4 Toll-like receptor 4
TNF-α Tumor necrosis factor-α
TNM  Tumor, node, metastasis
TPB  Theory of planned behavior
TURP Transurethral resection of the prostate
\( \dot{V}O_{2\text{max}} \) Maximal oxygen consumption
\( \dot{V}O_{2\text{peak}} \) Symptom-limited maximal oxygen consumption
WCRF World Cancer Research Fund
WHELS Women’s healthy eating and living study
WINS Women’s intervention nutrition study
WMD  Weighted mean difference
WTBS Weight training for breast cancer survivors
YES Yale exercise and survivorship
Chapter 1
Introduction

John Saxton and Amanda Daley

Abstract  The global burden of cancer has more than doubled during the last 30 years and with the continued growth and aging of the world’s population, it is expected to double again by 2020. While 5-year survival rates for some cancers remain very poor, an increasing number of people in economically developed societies are now surviving for at least 5 years after being diagnosed with some of the most common cancers. This means that the quality of cancer survival has become an important issue in the management of cancer patients. The cancer experience is widely acknowledged as a life-changing event and can be the trigger for reviewing personal health behaviours and making major lifestyle changes. For some cancers, a growing body of observational evidence suggests that a physically active lifestyle can be beneficial in terms of primary prevention and cancer mortality. Prospective intervention studies have also shown that regular exercise participation during and after cancer treatment is associated with higher levels of physical functioning and CV fitness, reduced feelings of fatigue and improved health-related QoL. Nevertheless, the specific benefits of habitual exercise are likely to vary as a function of cancer type and disease stage, treatment approach and current lifestyle of the patient. The aim of this book is to present the most up-to-date synthesis of scientific evidence gleaned from observational and intervention studies that have investigated the health benefits to cancer patients of engaging in a physically active lifestyle.

1.1 The Burden of Cancer

Cancer is an ‘umbrella term’ for a group of over 200 different diseases, in which cells of the body grow and divide in an uncontrolled way. This uncontrolled cellular growth often invades and destroys neighbouring tissues and can metastasize (via...
The disease affects people of all ages, the risk of developing most types of cancer increases with age. The recently published World Cancer Report showed that the global burden of cancer has more than doubled during the last 30 years and with the continued growth and aging of the world’s population, it is expected to double again by 2020 [1]. Worldwide, there were 12.4 million new cancer diagnoses in 2008, 7.6 million cancer deaths and 25 million people living with cancer [1].

Cancer is classified according to the tissue in which it originates. Carcinomas are cancers of the skin or tissues that line or cover the internal organs and include cancers of the lung, colon, prostate, breast and cervix. Sarcomas are cancers arising in bone, cartilage, fat, muscle, blood vessels and other connective and supportive tissues. Leukaemia is cancer that begins in the blood-forming tissues (e.g. bone marrow) and lymphoma (including multiple myeloma) originates in cells of the immune system [2]. Globally, lung cancer is the most commonly diagnosed cancer and cause of cancer-related death in men, whereas in women, breast cancer is the most common form of the disease and cancer-related death [1]. In both North American and European men, however, prostate, lung and colorectal cancers are the most commonly diagnosed forms of the disease, accounting for 56 and 50% of all incident cases, respectively. In North American women, breast, lung and colorectal cancers are the most commonly diagnosed, together accounting for 54% of all incident cases, in comparison to breast, colorectal and uterus cancers in European women (52% of all incident cases). Cancer mortality rates for North America and Europe are presented in Fig. 1.1, which illustrates that lung, colorectal, prostate (men) and breast (women) cancers are the leading causes of cancer-related death.

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Cancer survival statistics are based on the proportion of cancer patients who are still alive 5 years after diagnosis. Survival rates for some cancers (e.g. lung, liver, esophageal and pancreatic) are very poor and do not differ much between economically developed and developing nations [3]. These cancers are difficult to detect early and effective treatments are lacking. However, survival rates for cancers which can be detected early (perhaps through screening programs) and for which there are more effective treatments, differ considerably between poor and wealthy countries [3]. For Example, a global study of cancer survival statistics published in 2008 showed that the 5-year relative survival for breast cancer in women ranged from $\geq 80\%$ in North America, Sweden, Japan, Finland and Australia to $<60\%$ in Brazil and Slovakia and $<40\%$ in Algeria [4]. In addition, the 5-year relative survival rates for colorectal cancer were much higher in North America, Japan, Australia and western Europe than in Algeria, Brazil and eastern European countries, and PCa survival in North America was the highest in the world at over 90% [4]. There were also ethnic differences in survival rates within nations, with white cancer patients generally fairing better than their black counterparts. The increased numbers of people in economically developed societies who are alive for at least 5 years after being diagnosed with these common cancers means that the quality of cancer survival has become an important issue in the management of cancer patients.

1.2 Stages of the Cancer Experience

The cancer experience can be segregated into different stages (Fig. 1.2), and this needs to be considered when interpreting data from exercise studies in cancer populations. Although the experience of cancer wittingly begins at diagnosis, the impact of the disease on health and QoL is often experienced before this. Depending on the type of cancer that is diagnosed, this is usually followed by a treatment phase, which constitutes a period of medical treatment or AS (as in PCa patients). Cancer is usually treated with some combination of surgery, RT and/or drug treatments (including chemotherapy, hormone therapy and immunotherapy), the side-effects of which can significantly impair physical functioning and QoL. After the treatment phase, an increasing number of patients are now entering a recovery/rehabilitation phase, with the aim of regaining full or acceptable levels of health and physical function. However, a proportion of these patients will experience recurrent disease or will develop second primary tumours and will enter the treatment cycle once more (Fig. 1.2). For patients who are not eligible for curative treatments, the treatment phase becomes a palliative end of life phase, which for some can be a prolonged period of time and, in which the main aim is to relieve pain and maintain QoL.

The term ‘cancer survivor’ is frequently used for individuals who have ‘beaten’ cancer or at least been free of the disease for a minimum of 5 years (the latter perception is consistent with ‘cancer survivorship’ statistics, which use a
Fig. 1.2 Stages of the cancer experience. QoL: quality of life

5-year cut-point as a reference for survival). However, leading cancer organisations such as the ACS and the NCI in the USA have commented that people living with cancer should also be included in any definition of ‘cancer survivor’ [5]. Additionally, the NCI also believes that the term should be extended to family, friends and caregivers (‘secondary survivors’) who are affected by the cancer experience of a loved one. Whilst not including statistical data from secondary survivors in its reports, the NCI describes the term ‘Cancer survivor’ on its website as encompassing:

… the physical, psychosocial, and economic issues of cancer, from diagnosis until the end of life. It focuses on the health and life of a person with cancer beyond the diagnosis and treatment phases. Survivorship includes issues related to the ability to get health care and follow-up treatment, late effects of treatment, second cancers, and quality of life. Family members, friends, and caregivers are also part of the survivorship experience.

Despite the fact that cancer survival rates in economically developed societies are improving, cancer survivors are vulnerable to disease recurrence and are at increased risk of second primary tumours (in the same organ or at different sites), other chronic age-related conditions and poor mental health. These include osteoporosis, CV disease, diabetes, functional losses, depression and anxiety that can threaten independent living [6–8]. As a result, cancer survivors make greater demands on
health systems than the general population due to treatment follow-ups, screening for independent secondary cancers or permanent functional disabilities resulting from cancer treatment [9]. They also have a higher death rate from non-cancer causes than the general population [10].

1.3 Exercise and the Cancer Survivor

1.3.1 Cancer as a ‘Teachable Moment’

The cancer experience is widely acknowledged as a life-changing event [8], which can change a person’s outlook on life, alter their priorities and be the catalyst for major life-changing decisions. For this reason, it has been proposed that a cancer diagnosis could be a ‘teachable moment’ [8], defined as a point in a person’s life when they may be more motivated to spontaneously adopt risk-reducing health behaviours because of naturally occurring life transitions or health events [11]. The ‘teachable moment’ concept has been used in a variety of different health behaviour contexts, including smoking cessation, sexual behaviour, alcohol consumption, injury prevention and lifestyle change [11, 12]. For those diagnosed with cancer, it could be the trigger for reviewing health behaviours and making substantial lifestyle changes. It could also provide a window of opportunity for physicians and healthcare providers to promote the immediate and longer term benefits of healthy lifestyle behaviours, including an active lifestyle, in relation to wide-ranging health outcomes, in cancer patients and survivors.

1.3.2 Health Benefits of Exercise

Evidence for the use of exercise in the maintenance of optimal health and rehabilitation can be traced back to ancient cultures. As early as the ninth century BC, the ancient Indian system of medicine (Ayurveda) recommended exercise and massage for the treatment of rheumatism, and the Greek philosopher Hippocrates (‘the father of medicine’) acknowledged the virtues of exercise for physical and mental health in the fourth century BC. [13]. In more recent times, a body of epidemiologic research has demonstrated inverse associations of varying strength between habitual exercise and the risk of several chronic diseases, including coronary heart disease, thromboembolic stroke, hypertension, Type 2 diabetes mellitus, osteoporosis, obesity, anxiety and depression [14–16]. Additionally, a growing body of research during the last 20 years has provided ‘convincing’ evidence of an inverse association between PA and risk of colon cancer [17]. There is also evidence of a ‘probable’ inverse association between PA and risk of other cancers, including post-menopausal breast and endometrial cancer and limited ‘suggestive’ evidence of a similar association between PA and lung, pancreatic and pre-menopausal breast cancer [17].
Studies have also shown that regular exercise participation during and after cancer treatment is associated with higher levels of physical functioning and CV fitness, reduced feelings of fatigue and improved health-related QoL [18, 19]. Furthermore, recent observational research shows that habitual exercise in the recovery/rehabilitation phase after cancer treatment can have a positive impact on disease-free survival in breast and colorectal cancer patients [20–25]. The role of a physically active lifestyle in helping to maintain a desirable body weight could be important in this respect, as studies have shown that excess body weight is associated with poorer prognosis in breast, colorectal cancer and PCa patients [26–29]. Nevertheless, the specific beneficial effects of exercise are likely to vary as a function of cancer type and disease stage, treatment approach and current lifestyle of the patient [18]. Furthermore, the impact of exercise is also likely to be different across the different stages of the cancer experience: most research to date has investigated the effects of exercise in the recovery/rehabilitation phase and more limited evidence is available for the pre-treatment and treatment phases. The end of life phase is another time that exercise could have an important impact on QoL.

1.3.3 Exercise Terminology

‘Exercise’ and ‘PA’ are terms that are commonly used in the scientific literature. Exercise is more often used to refer to structured leisure-time physical activities, such as jogging, swimming and recreational sports, rather than to common activities of daily living which include walking and physical tasks performed in the home or work environment. The latter are more commonly categorised as PA. In 1985, definitions for PA and exercise were proposed by Caspersen et al. [30] to provide a framework in which studies could be interpreted and compared. They defined PA as ‘any bodily movement produced by skeletal muscles that results in energy expenditure’. Exercise, on the other hand, was defined as a sub-category of PA which is ‘planned, structured, repetitive and purposive’ and which has the objective of improving or maintaining one or more components of physical fitness. The potential limitations of these definitions were recently highlighted by Winter and Fowler [31], who pointed to shortfalls in relation to isometric exercise (static muscle actions) and argued that the two terms are interchangeable, and which one is actually used depends on the circumstances and context. For the purpose of this book, both exercise and PA are considered to mean any movement (or isometric exercise) of the skeletal muscles, either in the context of recreational (leisure time), occupational or usual activities of daily living, which increases energy expenditure.

Physical fitness and health-related fitness are other important terms that are often associated with habitual exercise participation. Whilst there is no universally agreed-upon definition of physical fitness (or its components), this term generally refers to the characteristics of an individual that permit good performance of a given task in a specified physical, social and psychological environment [32]. Physical fitness is influenced by genetic factors and is also sensitive to positive
change in people of all ages and initial physical fitness level as a result of exercise participation. Physical fitness can be broken down into smaller measurable components, such as aerobic power/endurance, muscular strength/endurance, speed/power, agility and flexibility. *Health-related fitness* is concerned with those aspects of physical fitness and psychological wellbeing that can be affected favourably by engagement in a physically active lifestyle. In a Scientific Consensus Statement [32], the components of health-related fitness were categorised into morphological, muscular, motor, cardiorespiratory and metabolic. Although this model includes the main physical dimensions of health-related fitness, it does not include the potential psychosocial health benefits that can result from habitual exercise participation in cancer survivors. Hence, a revised model, which encompasses both physiological and psychosocial health-related fitness components which are relevant to cancer survivors, is shown in Fig. 1.3. Additional components, such as ‘immunological’ and ‘molecular’, represent other biological pathways that could be positively influenced by habitual exercise participation and, as a consequence, could impact upon cancer health outcomes and QoL.

![Components of health-related fitness](image)

*Fig. 1.3* Components of health-related fitness
1.3.4 Exercise Guidelines for Cancer Survivors

Although definitive evidence-based exercise guidance is currently lacking, many studies have shown that exercise is safe and feasible for cancer patients and survivors, with little evidence so far of adverse effects. As cancer is such a diverse disease, however, it is unlikely that any future exercise guidance would be consistent across all cancer types. Furthermore, any evidence-based exercise guidance that is developed is likely to differ according to stage of the cancer experience. Nevertheless, public health recommendations for PA and exercise guidance for primary cancer prevention provided by prominent cancer organisations might also be appropriate for cancer survivors, particularly those who have been diagnosed and treated for colon or breast cancer.

In 1995, the US Centers for Disease Control and Prevention and American College of Sports Medicine’s landmark Consensus Statement on Physical Activity and Public Health recommended that every US adult should accumulate 30 min or more of moderate intensity PA on most, preferably all days of the week [14]. This report was updated in 2007 [15], but retained the same broad message about moderate intensity PA, except for identifying 5 days.week⁻¹ as the recommended minimum level. Alternatively, adults were advised that similar health benefits could be achieved from participation in vigorous-intensity aerobic exercise for a minimum of 20 min on 3 days each week. The recommendations for moderate intensity PA are consistent with the UK Chief Medical Officer’s report on PA published in 2004 [16]. Although no specific guidelines for the primary prevention of cancer were given in any of these reports, they did imply that health benefits could be gained from exercise participation at this level in relation to the risk of colon and breast cancer. Patients experiencing CRF may have to gradually work up to these levels and this issue is discussed further in Chapter 2.

The ACS, AICR/WCRF and CRUK have provided more detailed exercise advice for primary cancer prevention. These organisations endorse the original public health message of 30 min of moderate intensity PA on most, if not all, days of the week, but the ACS also states that 45–60 min of at least moderate intensity exercise on five or more days of the week may be optimal to reduce the risk of colon and breast cancer [33]. The AICR/WCRF in their 2007 Expert Report [17] recommends that as fitness improves, adults should aim for 60 min or more of moderate or 30 min or more of vigorous PA every day. For CRUK, 30 min of daily moderate intensity PA is considered the minimum level, with the recommendation that breast and bowel cancer risk can be further reduced by exercising more frequently, more intensely, for longer periods of time and throughout your lifetime [34].

For cancer survivors, ACS PA recommendations are similar to its advice for primary cancer prevention, although it is acknowledged that ‘few data are available to directly support this assumption’ [35]. Nevertheless, the ACS believes that following its guidance for [primary] cancer prevention may be helpful for reducing the risk of second cancers and other chronic diseases in cancer survivors. Additionally, exercise can be beneficial during treatment for cancer and can help the recovery
process and improve fitness during the recovery/rehabilitation phase after treatment [35]. CRUK highlights the potential health benefits of exercise in people recovering from cancer treatment in relation to reduced levels of stress, anxiety, depression and fatigue and increased levels of energy. While not recommending specific levels of exercise, it stresses the importance of building up exercise levels gradually (perhaps starting with gentle walking exercise) and highlights the importance of weight-bearing exercise for protecting against osteoporosis [34].

1.4 Levels of Evidence

1.4.1 General Overview

In the forthcoming chapters, a number of different methodological approaches have been used to assess the impact of a physically active lifestyle on health outcomes which are relevant to cancer patients. These include observational studies, such as surveys and case–control studies, and prospective intervention studies (RCTs and non-randomized trials). All types of study design have their merits and limitations, and these are briefly discussed here in the context of PA and cancer research.

1.4.2 Observational Studies

Observational studies do not investigate cause-and-effect relationships but associations between outcomes and ‘exposures’ of interest (e.g. self-reported habitual exercise) can be explored. Hence, the data from these types of studies should be interpreted in this context. However, survey research is the most common type of observational research, where information about individuals’ opinions, practices or behaviour is obtained through the use of interview or questionnaire methods. This information is then typically used to make comparisons or determine trends and so forth. Surveys have been used extensively in this field, for example, to explore cancer patients’ views and attitudes towards PA and their preferences for different types of PA. Several studies have also assessed PA behaviours, often alongside other health behaviours, in cancer patients. This kind of information can be useful in shaping the design of subsequent randomised controlled trials (see later) that assess the effectiveness of PA interventions in cancer patients.

Other commonly used observational designs are cohort (prospective and retrospective) and case–control studies. In prospective cohort studies, PA status is assessed at some baseline time-point before participants are followed-up (sometimes at regular time intervals) to see if they reach a pre-defined clinical end-point (e.g. cancer diagnosis, recurrent disease, cancer mortality). The frequency with which the outcome occurs is then compared between physically active and more sedentary participants to determine their relative chances of reaching the clinical end-point. Retrospective cohort studies, on the other hand, use pre-existing data on PA levels
and outcomes and are quicker (and cheaper) to conduct for diseases like cancer that can take several years to develop.

A limitation of cohort studies is that exercise levels might be influenced by sub-clinical (as yet undiagnosed) cancer which could bias the results. However, in some of the larger studies in this field, the robustness of the main findings has been checked by eliminating patients who reached the clinical end-point within a short-time period of assessing PA status. Other limitations include failure to account for all potentially confounding variables in the analysis (although in larger cohort studies, a greater number of potential confounders can be controlled for) and the timescale needed to follow-up large numbers of people over many years (prospective studies). The long timescale involved (sometimes many decades) can also result in differences in loss to follow-up between exposure groups.

Case–control (or case comparison) studies are another type of observational design, in which participants are selected on the basis of whether or not they have a particular disease. A number of disease cases are identified, before a matched (e.g. on the basis of age, sex) or unmatched comparison group is selected. Case–control studies are considered less scientifically robust than cohort studies and are frequently nested within larger cohort studies. In this type of design, participants are selected on the basis of their disease status rather than exposure, and the main outcome measure is the OR of exposure (odds of exposure in the cases divided by the odds of exposure in the controls). This type of study design has been used predominantly to assess the impact of a physically activity lifestyle on cancer risk (primary prevention) and may have limited applicability for PA studies in cancer survivors.

1.4.3 Qualitative Studies

Qualitative research can be used to gain insight into people’s attitudes, behaviours, value systems, concerns, motivations, aspirations or lifestyles. Thus, when there is a need to understand the context of a phenomenon or an individual’s perspective, qualitative methods can help researchers generate in-depth descriptive data. In qualitative research there is an emphasis on process or how and why things happen and how people make sense of their experiences as they interpret them. Given this, some research questions will be best answered using qualitative methods. Types of qualitative research include interviews, focus groups and participant observation. Until recently there were few qualitative studies in this field. It is encouraging to see more studies of this kind emerging in the literature since ‘consumer’ perspectives on issues related to PA and cancer will have an invaluable role to play in helping to advance knowledge and will help to ensure that the evidence accurately represents those people for whom it is supposed to serve.

1.4.4 Randomized Controlled Trials

RCTs represent the ‘gold standard’ in study design for establishing a cause-and-effect relationship between an intervention and an outcome [36]. In their simplest
form, RCTs involve the random allocation of participants to an intervention group or a standard treatment (e.g. usual medical care with or without placebo) control group, although multiple experimental groups can also be compared with each other and the control comparison group. This type of design allows the rigorous evaluation of a single variable (or complex intervention) in a defined patient group, as the assumption is that all confounding variables (known or unknown) are distributed randomly and equally between the intervention and the control comparison groups.

An increasing number of RCTs are investigating the effects of exercise interventions on important health outcomes in cancer survivors, and many of these studies have been discussed in the following chapters. Study outcomes often include health-related QoL, perceptions of fatigue, physical (and functional) fitness, exercise adherence and indices of psychological wellbeing. A commonly used QoL measure in cancer patients is the FACT-G scale, which was developed and validated in the USA [37]. It comprises 27 general questions which are divided into four primary QoL domains: (i) physical wellbeing, (ii) social/family wellbeing, (iii) emotional wellbeing and (iv) functional wellbeing. The FACT-G represents the generic core questionnaire and this is often supplemented with cancer-site specific items for studies of different cancer populations, e.g. FACT-L (lung), FACT-P (prostate), FACT-C (colorectal) and soon.

Non-randomised intervention studies have also been used to investigate the effects of exercise in cancer patients. Non-randomised parallel-arm trials (and single-group intervention studies) are subject to considerably more bias, as confounding variables are unlikely to be equally distributed between the groups and the participants who volunteer for a particular intervention (or who are assigned to the intervention by an experimenter) may have certain characteristics which differ from the wider population (known as selection or allocation bias). Hence, the results of such trials should be interpreted in this context.

To date, the RCTs that have been conducted in cancer survivors have generally not incorporated long enough follow-up assessments or are insufficiently powered to detect differences in clinical end-points such as disease-free survival or mortality between intervention and control groups. However, some RCTs have reported changes in circulating biomarkers of cancer risk, which could give some indication of the effects of an exercise intervention on disease recurrence risk in cancer populations. Further research is needed, however, to more firmly establish the biological plausibility of such biomarkers in relation to important clinical outcomes.

1.5 Dose–Response Issues

It is important to establish whether dose–response relationships exist between habitual exercise and health outcomes that are relevant to cancer survivors. Measurable units of exercise can be derived from knowledge of frequency, intensity (light, moderate or vigorous) and duration. Some combination of these factors can also be used
to calculate total volume of exercise over a given time period. Another important factor to consider is exercise modality (type). In the context of health, purposeful structured exercise is often classified into aerobic activities that generally utilise large skeletal muscle groups in a rhythmic fashion (aimed at improving cardiopulmonary function and increasing oxygen uptake) and resistance exercises, in which skeletal muscles generate torque against an external resistance (e.g. use of free weights, body resistance to increase muscular strength).

In prospective RCTs, the frequency, intensity and duration of supervised exercise can often be precisely defined and the main modalities of exercise training can be easily recorded. Where unsupervised exercise is performed in the home or community setting, exercise logs and more objective PA assessment tools (e.g. heart rate monitors, pedometers, accelerometers) can be used to quantify the exercise dose. In observational studies, however, PA is typically quantified from self-report questionnaires or structured interviews. Examples of the instruments used include the International Physical Activity Questionnaire [38], the Godin [39, 40] and the Stanford Seven-Day Physical Activity Recall Interview [41]. The most robustly designed observational studies provide external validation data for the PA instrument, for example, correlation coefficients for the association between the questionnaire data and more objectively collected PA behaviour (e.g. accelerometry).

Multiples of the MET is perhaps the most commonly used method to quantify the intensity of PA in observational studies. One MET is defined as the energy expended (or rate of oxygen consumed) by an average adult when sitting quietly and is usually expressed as a rate of oxygen consumption of approximately 3.5 ml kg\(^{-1}\) min\(^{-1}\). Thus, an individual who is performing an activity of 3 METs has an oxygen consumption which is three times higher than at rest. Using this method, exercise intensity is categorised into absolute terms as ‘light’ (<3 METs), ‘moderate’ (3–6 METs) or ‘vigorous’ (>6 METs). Compendium tables are available in the scientific literature (e.g. Ainsworth et al. [42]), which can be used to assign the MET level typically associated with a specific recreational, household or occupational task. When the intensity of self-reported physical activities (in METs) is then multiplied by the duration of specific physical activities, the total volume of PA in MET-h.week\(^{-1}\) (or MET-h.day\(^{-1}\)) can be determined and used to assess associations between different levels of PA and cancer-relevant outcomes. A major limitation of this approach is that it is impossible to discern the relative importance of exercise intensity on any observed benefits to the health outcomes under study from such a PA (volume) measurement. Thus, when a volume measurement such as MET-h.week\(^{-1}\) is used to quantify exercise dose, it is useful if the quantitative PA data are accompanied by additional information about the main types and intensities of exercise that the population under study were involved in.

In addition to MET-h.week\(^{-1}\), a wide range of other grading systems have been used to quantify PA dose from self-report and structured interview instruments and this can make comparisons between studies difficult. Examples include average MET-h.day\(^{-1}\), h.week\(^{-1}\), energy expenditure per week and frequency of sessions per
Introduction

1. Introduction

A week (or month). Furthermore, these and other methods (including average sitting time, activity estimates of most prominent lifetime job) are commonly used to grade the level of occupational PA. In other studies, PA levels have been graded using qualitative terms such as ‘very active’, ‘moderately active’ or ‘quite inactive’, which lack detail, are highly subjective and can make comparisons between studies virtually impossible.

1.6 Aims of This Book

The role of exercise and other lifestyle interventions for promoting improvements in key cancer health outcomes is increasingly being studied by research groups around the world. At present, we still have much to learn about the health impacts of regular exercise in different groups of cancer patients, during different phases of the cancer experience and after different treatment regimens. Nevertheless, the weight of current evidence supports the assertion that a physically active lifestyle can have a positive impact on a wide range of physical and psychological outcomes, with little evidence of adverse effects. The key aim of this book is to present the most up-to-date synthesis of scientific evidence gleaned from observational and intervention studies that have investigated the health benefits to cancer patients of engaging in a physically active lifestyle.

Twelve active and eminent researchers or research groups in this field from the USA, Canada and Europe have each contributed a chapter to this book. The chapters include empirical evidence from a diversity of study designs, ranging from large-scale population studies to much smaller scale laboratory-based studies of molecular mechanisms. A major objective was to focus mainly on evidence from human studies, although reference to animal studies has been made, where appropriate. Many cancers remain under-represented in the exercise literature but this book presents what is known now about the impact of exercise on some of the most commonly diagnosed cancers, including, breast, prostate, colorectal and lung cancer.

Exercise oncology is a relatively new and expanding research area and future research will improve knowledge in relation to a number of key issues, including the impact of specific exercise modalities in different cancer populations and during different phases of the cancer experience, the relative benefits of supervised and self-directed exercise programs and how to optimise compliance to exercise participation at different time-points in the cancer journey. We hope this book will be of use to a range of both academics and health professionals, such as clinical exercise physiologists, nutritionists/dieticians, health promotion advisors, public health commissioners, health psychologists and exercise leaders. Some readers may choose to read this book in its entirety, whilst others may only read the chapters that are of most interest. For this reason, each chapter has been designed to be standalone. Lastly, we hope that this book will provide impetus for further research in the field, so that ultimately, all cancer patients will have the opportunity to experience the benefits that exercise might have to offer to them.
References

Chapter 2
Exercise and Cancer-Related Fatigue Syndrome

Margaret L. McNeely and Kerry S. Courneya

Abstract  CRF is the most frequently reported symptom affecting up to 90% of cancer patients. CRF is distinguishable from normal tiredness in that CRF symptoms are severe, distressing, and are not relieved by rest or sleep. While the mechanisms and contributing factors that lead to CRF are unclear, good evidence exists for promoting exercise as an intervention to combat CRF. Currently, more than 20 RCTs have examined the effects of exercise on CRF scores. Despite methodological limitations and small sample sizes, the evidence suggests that exercise can improve CRF both during and after cancer treatments. Current guidelines for exercise prescription in this population recommend a progressive aerobic exercise program of 20–30 min. session^{-1}, 3–5 days. week^{-1} at a moderate intensity of 60–80% of MHR. Further research is needed that examines potential mechanisms by which exercise influences symptoms of CRF.

2.1 Introduction

CRF is defined as ‘a subjective feeling of tiredness, weakness or lack of energy’ [1] that interferes with usual functioning [2]. CRF is the most frequently reported symptom by cancer patients and is distinguishable from normal tiredness in that CRF symptoms are severe, distressing, and are not relieved by rest or sleep [2, 3]. CRF may result from cancer or its treatments and is almost universal in patients undergoing chemotherapy, radiation therapy, HSCT, or treatment with biological response modifiers [3, 4]. As the use of multi-modal treatments and dose-dense, intensity-dense treatment protocols has increased, so has the burden of CRF [3].

Recent attention has been directed toward the potential role of exercise as an intervention for cancer patients and survivors [5–7]. Despite evidence suggesting benefit of exercise for symptoms such as CRF, exercise remains an uncommon component of care in the clinical setting. In this chapter, we review the growing literature on CRF with a focus on exercise as an intervention in the management of CRF.

M.L. McNeely (✉)
Department of Physical Therapy, University of Alberta, Edmonton, AB T6G 2G4, Canada
e-mail: mmcneely@ualberta.ca

2.1.1 Incidence of Cancer-Related Fatigue

CRF has been reported through the continuum of the cancer experience from diagnosis to advanced stages of the disease [4]. While the estimated prevalence of frequent tiredness among the general population is reported to be 20–30% [8], CRF is estimated to affect 70–90% of cancer patients [9]. CRF may be an early symptom of malignant disease and is reported by approximately 40% of patients at diagnosis [3, 4]. CRF may continue for months or even years as a late or long-term effect following cancer treatment and is almost universal in patients with advanced disease [10–12]. The impact of CRF on QoL is often profound, as patients become too tired to participate in usual activities and normal social roles [13].

2.1.2 Etiology of Cancer-Related Fatigue

The mechanisms and contributing factors that lead to CRF are unclear. Multiple factors related to the tumor and/or its treatment such as abnormalities in energy metabolism, hormonal changes, chronic stress responses, anxiety and depressive disorders, anemia, and altered sleep patterns may lead to CRF [2, 14, 15]. CRF may also occur as a consequence of cancer-related symptoms such as pain, nausea, and dyspnea [16]. Furthermore, research suggests that inactivity leading to impairments in cardiorespiratory fitness and muscle function may be underlying mechanisms that may worsen and/or perpetuate CRF [17, 18]. To date, few studies have examined the physiological, behavioral, or biological basis of fatigue [19].

2.1.3 Conceptual Framework for the Study of Cancer-Related Fatigue

Mock et al. [20] developed a conceptual model to provide an organizing structure for studying the effects of nurse-directed exercise interventions on CRF. In this model, the individual’s goal is to respond or adapt to fatigue in order to conserve or preserve personal unity and integrity. Four conservation principles are proposed that include conservation of energy, structural integrity, personal integrity, and social integrity. In the conservation of energy principle, the aim is to reduce CRF by balancing energy resources with energy expenditure. Patients are provided with education materials on energy conservation and prescribed an exercise program to conserve or enhance energy capacity. In the conservation of structural integrity principle, the aim is to prevent or reverse the loss in physical functioning. This principle is addressed directly by the exercise program. The conservation of personal integrity principle emphasizes the concept of personal identity and sense of self. Exercise is used to help provide the patient with a sense of control over their health promotion. The fourth principle, conservation of social integrity, is concerned with the maintenance of normal social roles and QoL. Exercise is used to maintain or enhance
energy levels to facilitate continued social interactions. The four principles are used to guide the development of interventions and the selection of appropriate outcomes and measurement tools.

2.2 Assessment of Cancer-Related Fatigue

Fatigue may describe both the measurable decrease in the capacity for physical and mental work and the subjective mental state [2, 21]. Thus, the perception of fatigue may result from many factors related to physiological, psychological, or cognitive changes [19]. Current National Comprehensive Cancer Network guidelines recommend regular screening for the presence and severity of CRF [3]. According to the guidelines, patients reporting moderate to severe subjective CRF (i.e., a score of four or more on a visual analog scale of 0–10) should undergo a focused history and medical exam to address contributing factors such as pain, anemia, sleep disturbance, and lack of activity.

2.2.1 Clinical Syndrome of Cancer-Related Fatigue

Cella et al. [22] proposed criteria for the diagnosis of a clinical syndrome of CRF. In this syndrome, a patient is considered to have CRF if they present with six or more symptoms including significant fatigue. Some of the symptoms include diminished concentration, decreased motivation, post-exertional malaise, and non-restorative sleep. To meet the criteria for the clinical syndrome of CRF, symptoms must be present every day or nearly every day in a 2-week period, cause clinically significant distress or impairment, be a consequence of cancer, and not be related to a co-morbid psychiatric disorder. The authors have developed an interview guide to assist clinicians in the diagnosis of CRF.

2.2.2 Cancer-Related Fatigue-Specific Measurement Instruments

Minton and Stone [23] performed a systematic review of scales used for the measurement of CRF. The authors reported that the most widely used and best validated scales include the FACT-F, the EORTC Questionnaire – Fatigue subscale, and the FQ. The best choice of scale to use, however, will vary depending on factors related to patient characteristics, the setting, and time frame and fatigue dimensions of interest. As an Example, the 13-item FACT-F may be more appropriate for the research setting as it is sensitive to change and has established cut-points for determining both clinically significant CRF and the minimal important difference for change in CRF. Alternatively, the three-item EORTC – Fatigue subscale may be more feasible for the busy clinical setting. Features of some commonly used CRF-specific instruments are summarized in Table 2.1.
<table>
<thead>
<tr>
<th>Scale</th>
<th>Features</th>
<th>Domain(s) measured</th>
<th>Evaluation time frame</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC – Fatigue subscale</td>
<td>• Three-item uni-dimensional scale converted to a score/100</td>
<td>Physical fatigue</td>
<td>Fatigue over past week</td>
<td>• Benefit in clinical setting: brief and simple to administer</td>
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<tr>
<td></td>
<td>• Minimal time for completion</td>
<td></td>
<td></td>
<td>• Ceiling effect: questionable for use in palliative setting</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Cut-point score of 40/100 for clinically significant CRF suggested</td>
</tr>
<tr>
<td>FACT-F</td>
<td>• Thirteen-item uni-dimensional scale: 5-point Likert scale</td>
<td>Physical fatigue</td>
<td>Fatigue over past week</td>
<td>• Recommended for use with intervention studies in research setting</td>
</tr>
<tr>
<td></td>
<td>• Fatigue scale part of a 20-item anemia scale</td>
<td></td>
<td></td>
<td>• Can be used independently or administered with the FACT-General scale</td>
</tr>
<tr>
<td></td>
<td>• Higher scores = less fatigue</td>
<td></td>
<td></td>
<td>• Score of 34/52 cut-point for clinically significant CRF</td>
</tr>
<tr>
<td></td>
<td>• Time for completion: 5–10 min</td>
<td></td>
<td></td>
<td>• MCID: 3.0 points for Fatigue subscale</td>
</tr>
<tr>
<td>FQ</td>
<td>• Eleven-item multi-dimensional scale</td>
<td>Physical and mental fatigue</td>
<td>Fatigue over the last month versus when patient felt well</td>
<td>• Measures both subjective physical and mental fatigue</td>
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<tr>
<td></td>
<td>• Subscales: 7-item physical fatigue and 4-item mental fatigue</td>
<td></td>
<td></td>
<td>• Originally developed for use with chronic fatigue syndrome</td>
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<tr>
<td></td>
<td>• 5–10 min</td>
<td></td>
<td></td>
<td>• Useful for screening for CRF</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Cut-point for fatigue: &gt;4.0</td>
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<tr>
<td>Scale</td>
<td>Features</td>
<td>Domain(s) measured</td>
<td>Evaluation time frame</td>
<td>Comments</td>
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<tr>
<td>Revised PFS</td>
<td>• 27 items: 5 qualitative, 22 items on 11-point Likert scale&lt;br&gt;• Time to completion: ~15–20 min</td>
<td>Behavioral/severity; affective meaning; sensory; cognitive/Mood</td>
<td>Current fatigue</td>
<td>• Comprehensive, multi-dimensional scale&lt;br&gt;• Limitations: appropriate for use in individuals experiencing CRF</td>
</tr>
<tr>
<td>BFI</td>
<td>• Nine-item: 11-point Likert scale&lt;br&gt;• Time for completion: 5 min</td>
<td>Fatigue severity and interference</td>
<td>Past week; current; past 24 h</td>
<td>• Suggested cut-points for mild (score: 1–3), medium (score: 4–6), and severe fatigue (score: 7–10)</td>
</tr>
<tr>
<td>SCFS</td>
<td>• Fifteen-item: 5-point Likert scale&lt;br&gt;• Time for completion: 2–3 min</td>
<td>Physical, affective cognitive</td>
<td>Current fatigue</td>
<td>• Useful for screening&lt;br&gt;• Revised version: SCFS-6-item version that measures fatigue in past 2–3 days&lt;br&gt;• MCID: 5-point total scale; 0.8 per single item</td>
</tr>
<tr>
<td>MFSI</td>
<td>• Thirty-item: 5-point Likert scale&lt;br&gt;• Time for completion: 5–10 min</td>
<td>General, physical, emotional and mental fatigue, and vigor</td>
<td>Past week</td>
<td>• Validated in breast cancer patients undergoing treatment and mixed cancer population</td>
</tr>
<tr>
<td>Fatigue Symptom Inventory</td>
<td>• Fourteen-item multi-dimensional: 0–10 numeric rating scale&lt;br&gt;• Time for completion: 5 min</td>
<td>Measures: severity, frequency, diurnal variation, and interference</td>
<td>Past week and current fatigue</td>
<td>• Brief, multi-dimensional measure&lt;br&gt;• To be used in conjunction with the 30-item MFSI</td>
</tr>
</tbody>
</table>
2.3 Management Strategies For Cancer-Related Fatigue

CRF is seen as a multi-causal, multi-dimensional problem [24] and a difficult symptom to manage [25]. CRF is typically addressed by a multidisciplinary team that may include an oncologist, oncology nurse, psychologist, nutritionist, occupational and physical therapist, and exercise specialist. Successful multidisciplinary management of CRF requires an understanding of the role of the main adjunctive interventions [2]. In the following section, we present the findings of a number of systematic reviews and meta-analyses examining pharmacological, psychosocial, and exercise interventions.

2.3.1 Pharmacological Interventions

Anemia is a frequent side effect seen in patients undergoing adjuvant cancer treatment and fatigue is a symptom of anemia [2]. Erythropoietin and darbopoietin are agents that stimulate red blood cell production and are prescribed to improve anemia in patients receiving chemotherapy. Minton et al. [26] conducted a Cochrane systematic review examining pharmacological management of CRF and found evidence of benefit for CRF from both erythropoietin and darbopoietin. While helpful, however, the correction of anemia has not been found to improve CRF to the degree intended [27]. Furthermore, recent studies have raised safety concerns related to the increased risk of venous thromboembolism and mortality from these agents [28].

Methylphenidate is a mild central nervous system stimulant that is more commonly known as Ritalin. Methylphenidate is prescribed to children with attention-deficit hyperactivity disorder to reduce impulsive behavior and to facilitate concentration on work and other tasks [29]. In cancer patients, methylphenidate has been used to treat opioid-induced drowsiness, improve mood, and cognitive function [29]. In early pilot studies, methylphenidate was shown to improve CRF in advanced cancer patients and in melanoma patients undergoing interferon treatment [17, 18]. In their review, Minton et al. [26] reported the pooled results from two RCTs examining the effect of methylphenidate on CRF and found a small benefit from the use of the drug for CRF.

2.3.2 Psychosocial Interventions

Psychosocial interventions are administered to influence or change cognition, emotion, behavior, the social environment, or a combination of these, with the ultimate goal to decrease CRF [2, 16]. Interventions may be structured or individually tailored and often include cognitive and behavioral strategies to help reduce stress, enhance adaptive coping skills, and/or increase emotional support [29].

Jacobsen et al. [16] performed a meta-analysis of nonpharmacological interventions for CRF. The meta-analysis included 30 trials with 3,443 participants. The
review included both psychosocial interventions and activity-based interventions. The authors reported finding few studies with severe fatigue as an eligibility criterion. The pooled results from 18 studies examining psychological interventions showed a very small significant effect on CRF (ES: –0.10; 95% CI: –0.02 to 0.18), while the pooled results from 12 studies examining activity-based interventions showed a nonsignificant effect on CRF (ES 0.05; 95% CI: –0.19 to 0.08).

Luebbert et al. [30] performed a meta-analysis of 15 RCTs examining the effect of relaxation training in cancer survivors. The authors reported that relaxation training in cancer patients resulted in significant improvements in blood pressure, pulse rate, nausea, pain, depression, tension, anxiety, mood, and hostility, but not CRF. The pooled data from two studies with 150 participants showed a potentially small but insignificant effect of relaxation therapy on CRF (ES: –0.24; 95% CI:–0.56 to 0.09).

2.3.3 Exercise Interventions

Over the past number of years, there has been increasing research evidence supporting the efficacy of exercise as an intervention both during and following cancer treatment [5–7, 31, 32]. More recently, Cramp and Daniel [33] performed a systematic review and meta-analysis examining the effect of exercise on symptoms of CRF. The meta-analysis included 22 comparisons with 1,662 participants. In the review, the authors reported that the majority of studies (n = 16) were carried out on participants with breast cancer and that few studies focused on CRF as the primary study endpoint. The pooled results showed a small but beneficial effect of exercise on symptoms of CRF when all studies were combined (SMD: –0.23; 95% CI: –0.33 to –0.13) and a slightly larger effect when examining the breast cancer sub-group alone (SMD: –0.34; 95% CI: –0.49 to –0.23). The authors also reported a slightly larger ES for studies carried out following cancer treatment (SMD: –0.37; 95% CI: –0.55 to –0.18) when compared to studies carried out during anti-cancer treatment (SMD: –0.18; 95% CI: –0.32 to –0.05).

Although the findings of the review by Cramp and Daniel [33] demonstrated benefit from exercise for CRF, there was considerable clinical heterogeneity (diversity) between studies in terms of the type of cancer, mode and intensity of exercise, and timing of the exercise intervention. The individual study results included in the meta-analyses showed variability in ES ranging from small to large and from beneficial to harmful effects. Thus, the overall finding of a small positive effect of exercise on CRF must be interpreted with caution, as exercise may prove to be more or less helpful based on the type of cancer, fatigue level, timing of the intervention, and type of exercise program.

In the following section, we present the findings of systematic reviews and meta-analyses examining the effect of exercise interventions on CRF in specific patient populations. Further details on these published meta-analyses and systematic reviews are provided in Tables 2.2 and 2.3, respectively.
<table>
<thead>
<tr>
<th>Study author, year/#</th>
<th>RCTs/CCTs</th>
<th>Selection criteria</th>
<th>Tumor groups included</th>
<th>Exercise intervention</th>
<th>Results/key findings on CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramp and Daniel [33]</td>
<td>RCTs</td>
<td>All cancer groups</td>
<td>• Aerobic exercise: 19 studies</td>
<td>• Small statistically significant beneficial effect when all studies combined</td>
<td></td>
</tr>
<tr>
<td>28 RCTs</td>
<td>Studies carried out during adjuvant cancer treatment, post-treatment or palliative care</td>
<td>• Resistance exercise: two studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Aerobic and resistance combined: three studies</td>
<td>• Small statistically significant beneficial effect in breast cancer sub-group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Aerobic and flexibility: two studies</td>
<td>out post-treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Yoga: two studies</td>
<td>• Slightly larger effect in studies carried</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Seated exercise: one study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Markes et al. [34]</td>
<td>Controlled clinical trials</td>
<td>Breast cancer</td>
<td>• Aerobic exercise: four studies</td>
<td>• Nonsignificant effect during adjuvant breast cancer treatment</td>
<td></td>
</tr>
<tr>
<td>4 RCTs and 1 CCT</td>
<td>Studies carried out during adjuvant breast cancer treatment</td>
<td></td>
<td>• Combined aerobic and resistance: one study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McNeely et al. [31]</td>
<td>RCTs only</td>
<td>Breast cancer</td>
<td>• Aerobic exercise: four studies</td>
<td>• Moderate statistically significant beneficial effect in studies during and following breast cancer treatment</td>
<td></td>
</tr>
<tr>
<td>6 RCTs</td>
<td>Studies carried out during and following breast cancer treatment</td>
<td></td>
<td>• Combined aerobic and resistance: two studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study author, year/ref.no studies examining CRF</td>
<td>Selection criteria</td>
<td>Tumor groups included</td>
<td>Exercise intervention</td>
<td>Results/key findings on CRF</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<td>-----------------------</td>
<td>----------------------------</td>
<td></td>
</tr>
<tr>
<td>Thorsen et al. [36] Published studies</td>
<td>PCa</td>
<td>• Aerobic exercise: one study</td>
<td>• One RCT reported a statistically significant beneficial effect from resistance exercise training in men receiving ADT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 studies including 3 RCTs</td>
<td>Studies carried out during or after PCa treatment</td>
<td>• Resistance exercise: two studies • Combined aerobic and resistance: one study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiskemann and Huber [39] Published studies</td>
<td>All cancer groups</td>
<td>• Aerobic exercise: three studies</td>
<td>• Beneficial effects from exercise post-treatment in two single-group studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 studies including 2 RCTs</td>
<td>Studies carried out during or after HSCT</td>
<td>• Combined aerobic and resistance exercise: one study</td>
<td>• Nonsignificant effect from exercise carried out during high-dose chemotherapy in one RCT • Nonsignificant effect from exercise in multiple myeloma patients before, during, and after HSCT in one RCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowe et al. [44] Published studies</td>
<td>All cancer groups</td>
<td>• Seated exercise: one study</td>
<td>• Statistically significant decrease in physical fatigue in one single-group study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 studies including 1 pilot RCT</td>
<td>Studies examining palliative cancer patients with a life-expectancy of less than 12 months</td>
<td>• Combined aerobic and resistance exercise: one study</td>
<td>• Statistically significant slower rate of increase in CRF in exercise group when compared to control group in one RCT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.3.3.1 Breast Cancer

Markes et al. [34] performed a meta-analysis of randomized and controlled clinical trials examining exercise interventions for breast cancer patients undergoing adjuvant cancer therapy (see Chapter 3). The pooled results of five studies with 317 participants demonstrated a nonsignificant effect of exercise on CRF (SMD: –0.12; CI: –0.37, 0.13). McNeely et al. [35] performed a meta-analysis of RCTs examining exercise interventions for breast cancer both during and following cancer treatment [31]. The pooled results of six studies examining the effect of exercise on CRF demonstrated a moderate beneficial effect (SMD: –0.46; 95% CI –0.23 to –0.70). The authors reported, however, that this overall effect was largely the result of positive effects found in two studies performed following cancer treatment. Thus, in breast cancer, this evidence suggests that the relative benefit of exercise on CRF, in the short term, may be dependent on whether the exercise intervention is delivered during or following cancer treatment.

2.3.3.2 Prostate Cancer

Thorsen et al. [36] performed a systematic review of studies examining the effect of exercise in PCa survivors. The review included four studies with 260 participants that examined CRF as an outcome. The review did not provide information on the methodological quality of the included studies. Although all studies demonstrated reductions in CRF, only one study [37] reported a statistically significant effect of exercise on CRF. Segal et al. [37] studied the effect of resistance training in 155 men with PCa receiving ADT. Following 12 weeks of supervised resistance training carried out 3 times week, men in the exercise group experienced a significant improvement in CRF compared to the usual care group. These differences remained regardless of whether men were treated with curative or palliative intent and also remained whether ADT had been received for less than or more than 1 year.

In a more recent RCT, not included in the Thorsen review, Segal et al. [38] compared the effects of a 24-week resistance or aerobic training regimen versus usual care in 121 men with PCa receiving RT. The authors reported that both resistance ($p = 0.01$) and aerobic exercise ($p = 0.004$) attenuated the decline in CRF over the short term compared to the usual care group. Resistance exercise was found to produce longer term effects on CRF ($p = 0.002$) and additional benefits for QoL, strength, triglycerides, and body fat. Thus, this evidence supports the benefit of exercise, particularly resistance exercise, for symptoms of CRF in men undergoing treatment for PCa.

2.3.3.3 Hematopoietic Stem Cell Transplantation (HSCT)

Wiskemann and Huber [39] performed a systematic review of all types of published studies (controlled and uncontrolled trials) examining the effect of exercise in patients undergoing or following HSCT. The authors reported findings of 15 published studies, of which four reported outcomes for CRF. Of these four studies, two
studies were uncontrolled single-group studies [40, 41] and two studies were RCTs [42, 43]. Wilson et al. [40] found that a home-based aerobic exercise intervention improved the severity of CRF in 17 long-term HSCT survivors. Carlson et al. [41] found a beneficial effect from exercise on CRF following a 12-week supervised outpatient exercise program for 12 HSCT patients who had completed treatment. The authors reported that this positive effect was maintained over a 1-year follow-up period. Dimeo et al. [42], using an RCT design, found that exercise prevented reductions in CRF during high-dose chemotherapy and HSCT; however, no statistically significant difference was found between the exercise and control groups \((N = 59)\). Coleman et al. [43], in another RCT, examined a 6-month home-based exercise program for 24 multiple myeloma patients before, during, and after HSCT and reported no significant differences in CRF between exercise and control groups. While results from these studies suggest potential benefit of exercise for interventions delivered following HSCT, the methodological limitations and small sample sizes of the studies performed to date highlight the need for more rigorous research.

### 2.3.3.4 Advanced Cancer

Lowe et al. [44] performed a systematic review examining the benefit of PA in palliative cancer patients. The authors identified six studies with a total of 84 participants. Three studies were single case reports, two studies were pilot uncontrolled single-group trials and one study was a pilot RCT. The methodological quality of the included studies in the review was considered low and only two of the six studies reported data related to the outcome of CRF. Oldervoll et al. [45] in an uncontrolled single-group study \((N = 34)\) demonstrated a significant decrease in the physical fatigue subscale and a borderline significant decrease in total fatigue score of the Fatigue scale. Headley et al. [46] in an RCT \((N = 38)\) reported that the exercise group had a statistically significant slower rate of increase in CRF than the control group. The preliminary findings suggest that exercise may attenuate the natural progression of increasing CRF in palliative cancer patients. As such, to elucidate this potential effect, future research using a controlled trial design is recommended.

### 2.3.4 Combined Interventions for Cancer-Related Fatigue

A number of studies have included exercise as a component of a combined intervention to address CRF. Courneya et al. [47] performed an RCT examining the benefit of group psychotherapy with and without a home-based exercise program. Twenty-two group psychotherapy classes consisting of 108 cancer patients and survivors were randomly assigned to group psychotherapy alone (11 classes; \(n = 48\)) or group psychotherapy plus exercise (11 classes; \(n = 60\)). The exercise group was asked to exercise independently at a moderate intensity for at least 20–30 min each time, 3–5 times.week\(^{-1}\) for 10 weeks (the length of the psychosocial program). A significant effect was found in favor of the combined exercise and group psychotherapy intervention for CRF when compared to group psychotherapy alone \((p = 0.04)\).
Heim et al. [48] performed an RCT in 63 breast cancer survivors with post-treatment CRF [48]. Patients were randomized to a complex rehabilitation program with or without a self-directed exercise program. The complex rehabilitation program included education, physiotherapy, group exercises, and psychosocial intervention. The self-directed exercise program consisted of upper and lower body resistance exercise and an aerobic walking program. CRF was measured using the FACT-F and the MFI. CRF was found to improve in both groups over time during the intervention period, with significant differences in favor of the self-directed exercise program emerging at the 3-month follow-up (FACT-F: \( p = 0.003 \); MFI: \( p = 0.028 \)).

Courneya et al. [49] conducted an RCT in 55 mild-to-moderately anemic patients with solid tumors. Patients were randomized to either anemia treatment with darbopoietin alone (\( n = 29 \)) or darbopoietin plus aerobic exercise training (\( n = 26 \)). The exercise group performed aerobic exercise training 3 times week\(^{-1} \) at 60–100% of baseline exercise capacity for 12 weeks. Borderline significant differences were found in favor of the exercise group for Hb response and darbopoietin dosing. Although significant improvements were found for CRF in both groups over time, there were no statistically significant between-group differences in CRF. The authors reported that while the addition of exercise to darbopoietin may result in a faster Hb response, and thus earlier attenuation of patient symptoms, these potential benefits may be offset by the recent data on safety concerns with the use of these agents.

### 2.4 Special Considerations for Exercise Testing and Programming

In the next section, we focus on some special considerations for exercise testing and programming for patients with CRF. These considerations are based on current research evidence as well as our clinical experience and from the literature on fatigue in other chronic conditions such as arthritis, heart failure, and chronic fatigue syndrome.

#### 2.4.1 Screening for Exercise Participation

All patients with CRF should be carefully reviewed by an oncologist prior to initiating exercise testing. The evaluation should include a history and physical examination to identify any medical problems that may limit or preclude participation in exercise. Guidelines that address safety and specific procedures for both exercise testing and prescription have been published previously by a number of authors [35, 50, 51]. It is important to note that cancer survivors with CRF may require medical supervision of exercise testing and additional monitoring during exercise sessions [35].
2.4.2 Exercise Testing

Cancer patients with CRF may present with differing degrees of functional capacity, therefore exercise testing is useful in evaluating objective components of physical fatigue. In the patient with CRF it may be difficult to determine the best method of exercise testing as fatigue may preclude optimal testing and overexertion may lead to an exacerbation of symptoms. Therefore, exercise testing may need to be modified or adjusted based on the severity of CRF and the physical presentation of the patient. If possible, exercise testing should include measures of body composition, cardiorespiratory fitness, muscular strength and endurance, and flexibility. Routine follow-up testing is recommended to monitor functional status as not all cancer patients with CRF will show the same response to exercise or the same rate of change in symptoms [51].

Cardiorespiratory fitness is normally best assessed using the gold standard test of maximal oxygen consumption (\(\dot{V}O_{2\text{max}}\)) [52]. This maximal testing, however, may not be feasible or appropriate for cancer patients with CRF. Modified testing using submaximal or field tests are indirect methods that are designed to estimate \(\dot{V}O_{2\text{max}}\) [52]. The most widely researched of these tests is the 6-min walk test. This field test measures the total distance walked in 6 min and is most reflective of activities of daily living [53]. The 2-min walk test has been proposed for populations who are not able to ambulate for 6 min and thus may be more appropriate for advanced cancer patients or those with profound CRF [53]. The test was designed to be performed in an enclosed corridor and measures the distance covered in 2 min. Rates of perceived exertion (using Borg scale), oxygen saturation (using an oximeter), and heart rate are monitored during the test [53] and provide feedback on subjective and objective responses to the test. The 2-min walk test has been tested in individuals with chronic heart failure, COPD, chronic airflow limitation, and neurological impairment [53].

Performance-based tests provide an alternative to traditional exercise testing methods. These tests are designed to objectively assess a number of dimensions relevant to functional actions. As an Example, the Senior Fitness Test consists of six test items (chair sit-to-stand, arm curls, chair sit-and-reach, back scratch for flexibility, 8-ft up and go, and 6-min walk test) that measure the underlying physical parameters (i.e., health-related fitness components) associated with functional ability [54]. The Continuous Scale Physical Functional Performance Test (16 items) is an alternative test that was designed to mimic activities of daily living and objectively measure upper body strength, lower body strength, flexibility, balance and coordination, and endurance [55].

2.4.3 Exercise Programming

In general, exercise programs for cancer patients and survivors have closely followed the published guidelines of the American College of Sport Medicine [52]. Numerous exercise guidelines have been published for the cancer population; however, only the guidelines developed by the NCCN have specifically addressed CRF
These exercise guidelines recommend a progressive aerobic exercise program of 20–30 min session\(^{-1}\), 3–5 days week\(^{-1}\) at a moderate intensity of 60–80% of MHR [3]. The recommendation of an aerobic exercise intervention is based on the consistent positive effects shown in research studies. The exercise prescription for CRF, however, may need to include all or a combination of the key components of health-related fitness: cardiorespiratory fitness (aerobic training), muscular strength and endurance (resistance training), and flexibility training. As evidence in the literature suggests, the optimal exercise prescription for CRF will likely vary depending on the patient’s cancer type and stage, current cancer treatment, and degree of CRF. Despite potential variations, a more conservative approach to exercise programming is likely warranted for those with CRF.

2.4.3.1 Prescription Considerations for Patients with Poor Functional Capacity

In some patients with CRF, functional status may be so impaired that excessive load or stress may occur with basic activities of daily living. In these patients, it may be advisable to start with range of motion and/or stretching exercises that are less likely to exacerbate existing CRF and progress toward more demanding exercise over time. The goal, however, should be to improve physical functioning to eventually allow for performance of exercise at an adequate training stimulus to improve cardiorespiratory and muscular fitness.

One method that has been successfully used with stable heart failure patients prescribes exercise based on baseline functional capacity and clinical status [56]. Those patients with functional capacity (\(\dot{V}O_2\text{peak}\)) above 17.5 ml kg\(^{-1}\).min\(^{-1}\) are prescribed three to five exercise sessions per week for 20–30-min duration similar to the recommendations proposed by the NCCN. Patients with a \(\dot{V}O_2\text{peak}\) of below 10.5 ml kg\(^{-1}\).min\(^{-1}\), however, are prescribed exercise starting with 5–10 min daily, while those with a \(\dot{V}O_2\text{peak}\) between 10.5 and 17.5 ml kg\(^{-1}\).min\(^{-1}\) are prescribed 1–2 sessions.day\(^{-1}\) of 15 min each. In this method, exercise is progressed through three stages of progression: (1) initial; (2) improvement; and (3) maintenance. In the initial phase intensity is kept low (e.g., 40–50% \(\dot{V}O_2\text{peak}\)) until a duration of 10–15 min is achieved. During the next stage, the improvement stage, the primary focus is on increasing exercise intensity from 40 to 80% \(\dot{V}O_2\text{peak}\) as tolerated. A secondary goal of this stage is to progress the duration of sessions from 15 to 20 min and even up to 30 min if possible. The maintenance phase begins after 6 months of training with the focus on maintaining exercise capacity. While this method has not been tested in the cancer population, it provides some guidance for prescribing exercise for more symptomatic individuals.

2.4.3.2 Intermittent or Interval Exercise Training

Patients with CRF may perceive energy reserves to be nearly depleted with normal daily activities and may be unable to sustain regimens of continuous exercise.
Exercise and Cancer-Related Fatigue Syndrome

Interval exercise training is an alternative method used to improve cardiorespiratory fitness. In practice, the interval session consists of short work periods of higher intensity work (e.g., 30 s) followed by a recovery phase (e.g., 60 s). This approach allows for a higher intensity or volume of exercise than would be possible with a continuous exercise protocol. Researchers have used intermittent or interval training for patients during chemotherapy treatment [57, 58] or immediately following bone marrow transplantation [42] as a way of accumulating exercise volume. Although research examining this form of training is limited, benefit has been demonstrated from interval training in outcomes such as body composition and functional capacity and in reduced hospital stay [6].

2.4.3.3 Muscular Fitness Training

Muscular strength and endurance training are particularly important to attenuate both sarcopenia and disease-related declines in muscle mass [59] that may present as muscular fatigue. Deficits in muscular strength and endurance can greatly impair an individual’s functional capacity and ability to carry out activities of daily living. Thus, muscular strength training with the goal to restore skeletal muscle mass may be an important step for patients before initiating an aerobic exercise training program.

A resistance exercise training program can be designed using elastic bands or light weights and/or may incorporate repetitions of specific functional tasks (e.g., repeated sit-to-stand from a chair). In terms of intensity, a program with lighter loads and higher repetitions may be more appropriate as a starting point to avoid secondary muscle soreness. Specific muscle groups can be targeted and single limb exercise and/or supported positions can be prescribed to avoid exacerbating fatigue. The recovery period or rest time between exercises, sets, and sessions is a component of the program that may need to be lengthened, particularly in the first few weeks of an exercise program, to allow for adequate recovery [35]. Initially this may involve spacing exercises or sets of exercises throughout the day and gradually reducing the recovery time between exercises/sets as a progression variable.

2.4.3.4 The Training Index

For CRF patients with better performance status, the exercise prescription may start by encouraging a more active lifestyle (e.g., take the stairs, walk instead of driving) with the goal of increasing daily PA to levels advocated by public health guidelines. The potential health benefits of increased PA have been long recognized even when minimal changes in cardiorespiratory fitness occur [52]. The training index is a form of monitoring that can be used to help the patient to progress total activity. Originally developed for use with cardiac patients, this method has also been used successfully in patients with rheumatic disease and fibromyalgia [60]. In this technique, the pulse rate taken during exercise is divided by the individual’s MHR (i.e., 220 minus person’s age) and multiplied by the number of minutes of exercise to
yield a training index for that session of exercise. At the end of the week, the daily training index values are added up to give a total for the week. The goal is to progress to the recommended number of units of 42–90 week$^{-1}$ that are needed to maintain adequate cardiorespiratory fitness [60]. The index is advantageous for patients with low activity levels and varying levels of energy and provides a quantitative method to progress activity over time (Table 2.4).

### Table 2.4 Training index

<table>
<thead>
<tr>
<th>Session</th>
<th>Pulse (a)</th>
<th>MHR (b)</th>
<th>Intensity (c) = (a)/(b)</th>
<th>Exercise duration (d) (min)</th>
<th>Training index = (c) × (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>105</td>
<td>165</td>
<td>0.63</td>
<td>10</td>
<td>6.3</td>
</tr>
<tr>
<td>Wednesday</td>
<td>115</td>
<td>165</td>
<td>0.70</td>
<td>10</td>
<td>7.0</td>
</tr>
<tr>
<td>Saturday</td>
<td>100</td>
<td>165</td>
<td>0.61</td>
<td>15</td>
<td>9.15</td>
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<tr>
<td>Weekly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22.45</td>
</tr>
</tbody>
</table>

### 2.4.3.5 Pacing

Patients with CRF should have a plan that includes both the proscription and prescription of exercise and activity. Patients may be resistant to exercise due to past experiences of symptom flairs from exercise. Education on the need for a slow progression of exercise to ameliorate physical function may ease concerns. Although no studies have specifically examined levels of exercise or activity that trigger exacerbations in CRF, efforts to pace activity within and outside of the exercise program and avoid overexertion should be encouraged. Furthermore, feedback during and following exercise sessions, as well as 24 and 48 h after exercise, is required for appropriate pacing of the program.

### 2.5 Summary and Conclusions

CRF affects approximately 70–90% of cancer patients. While the mechanisms and contributing factors that lead to CRF are unclear, good evidence exists for promoting exercise as an intervention to combat CRF. Currently, more than 20 studies have examined exercise using an RCT design. The evidence suggests that exercise will improve CRF during and after cancer treatments although few studies have
focused on patients with severe CRF. Exercise testing and prescription in cancer survivors with CRF must take into account the extent of CRF and any morbidity caused by treatments. Current guidelines for exercise prescription in this population recommend a progressive aerobic exercise program of 20–30 min.session$^{-1}$, 3–5 days.week$^{-1}$ at a moderate intensity of 60–80% of MHR [3]. Research is needed examining the effects of exercise on CRF with physical, behavioral, biologic, and hematologic measures taken serially over time [14].

Acknowledgment Kerry S. Courneya, Ph.D., is supported by the Canada Research Chairs Program and Research Team Grant from the NCI of Canada with funds from the Canadian Cancer Society and the Sociobehavioral Cancer Research Network.

References


Chapter 3
Exercise as an Intervention During Breast Cancer Treatment

Martina Markes

Abstract  Exercise is becoming an integral part of breast cancer rehabilitation. A growing body of evidence indicates that women experience improved health-related physical fitness and reduced fatigue through exercise, not only after breast cancer treatment has finished but during treatment. In this chapter, a systematic review is presented that summarises the findings of controlled trials that have examined the effects of exercise interventions on health outcomes in women undergoing treatment for breast cancer. The potential for adverse events is also discussed. If the benefits gained from participation in exercise programmes are to be maintained over the course of cancer survivorship, sustained exercise participation is essential and this chapter will explore issues related to adherence in women undergoing treatment for breast cancer. Additionally, the chapter will describe how exercise opportunities (tailored to the needs of breast cancer patients) are implemented within the community in Germany. This provides an example of how exercise programmes for cancer patients can be integrated with organised sports programmes.

3.1 Introduction

Approximately 430,000 and 182,000 new cases of breast cancer are diagnosed each year in Europe [1] and in the USA [2], respectively. The principal treatments for breast cancer are surgery, chemotherapy, RT and hormonal therapy and evidence suggests that these are very effective for improving disease-free survival and overall survival. However, these therapies can compromise women’s physical, mental or social health.

3.1.1 Impact of Breast Cancer Treatment

During breast cancer treatment, physical health can be impaired due to the illness itself or treatment modalities used and because of the ‘detraining’ effects
of sedentary habits. Health-related physical fitness is likely to decline because of physiological changes associated with breast cancer treatment, such as an insufficient oxygen supply (e.g. due to anaemia) or an insufficient blood supply to exercising muscles (e.g. due to cardiotoxic effects of anticancer treatment). Second, weight gain often occurs in women as a side effect of treatment, especially adjuvant chemotherapy and some forms of hormonal therapy (see Chapter 5). The observed pattern of weight gain is typically characterised as gain in weight without a concomitant gain in lean tissue [3]. Additionally, CRF is a health-related problem that affects 70–100% of all cancer patients. Fatigue is defined as a distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity [4] and interferes with usual functioning (discussed further in Chapter 2). Finally, women who receive adjuvant treatment for breast cancer may be at increased risk of osteoporosis, which can be attributed not only to the menopause, but also to ovarian failure from systemic chemotherapy, or the use of drugs such as aromatase inhibitors [5]. Vertebral body and hip fractures in breast cancer patients may result in substantially decreased QoL due to disabling chronic pain, loss of mobility and loss of independence [5]. Adjuvant treatment for breast cancer might also compromise mental health in terms of emotional distress, anxiety and depression [6–8], as well as cognitive impairment with symptoms such as difficulties with memory, concentration and language [9–11] of particular concern.

Proper management of the multiple symptoms resulting from cancer and its treatment is important, as symptoms can significantly distress patients and interfere with day-to-day functioning. Furthermore, such symptoms might delay treatment or lead to premature treatment termination [12, 13]. If treatment-related symptoms become so severe that patients abandon important (and sometimes potentially curative) therapies or if they cause treatment delays, they may diminish the chance of long-term remission or cure, and thus can directly affect survival [12]. Residual treatment-related symptoms can also limit vocational activities and inhibit social interaction [12].

3.1.2 Physical Activity Behaviours

Health behaviours such as PA that could work as self-management strategies in the day-to-day management of patients can be adversely affected by the stress associated with a breast cancer diagnosis and treatment. Indeed, research suggests that PA declines during receipt of adjuvant breast cancer treatment [14–16], particularly when adjuvant treatment is administered over a prolonged period of time. During and after cancer treatment patients may be instructed by health professionals to rest and to avoid PA. Experience shows that even regular exercisers who express their need to exercise during cancer rehabilitation are sometimes instructed to reduce their exercise levels or to stop exercising altogether. A decline in PA can be a significant
concern and there is the possibility that a lower level of PA could persist beyond the period of adjuvant treatment.

PA behaviour at the population level is considered to be inadequate across European Union countries [17]. The prevalence of sufficiently active adults assessed in a large multi-national survey was approximately 30% across the EU-member nations. Furthermore, women were less likely than men to be sufficiently active and the likelihood of being sufficiently active generally decreased in men and women with increasing age [17]. This indicates that even if the decline in exercise participation during adjuvant treatment for breast cancer is followed by recovery to pre-diagnosis levels after the conclusion of treatment, exercise participation may still be sub-optimal.

Sedentary habits and bed rest may further accentuate the adverse physiological changes associated with cancer treatment, resulting in more severe atrophy of the skeletal muscles and deleterious effects on the CV system. Indeed, one study reported that in older adults, 10 days of bed rest led to large amounts of skeletal muscle loss, particularly in the lower extremities, and this was greater than that observed in younger individuals after 28 days [18]. Another study [19] showed that prolonged bed rest of 2 months caused microcirculatory endothelial dysfunction, indicative of CV deconditioning.

According to the updated American College of Sports Medicine exercise recommendations [20], adults need moderate intensity aerobic (endurance) PA for a minimum of 30 min on 5 days each week or vigorous-intensity aerobic PA for a minimum of 20 min on 3 days each week. In addition to endurance PA, every adult should perform activities that maintain or increase muscular strength and endurance a minimum of 2 days each week.

Considering the adverse health effects of breast cancer and its treatment sequelae, coupled with reduced PA levels and the negative physiological impact of prolonged inactivity, exercise interventions may be particularly appropriate during adjuvant cancer treatment. This chapter seeks to highlight the benefits for physical and mental health that might be experienced by women who exercise during treatment for breast cancer, as well as the potential for adverse events. A second focus of this chapter will be the implementation of exercise programmes for women with breast cancer in organised community sports settings.

### 3.2 The Evidence Base for Exercise: A Systematic Review

Women, clinicians and health policy makers need reliable, up-to-date information from controlled trials on the benefits and potential adverse effects of exercising during adjuvant cancer treatment to allow them to make evidence-based decisions about treatments. At present, a diverse range of primary studies exists in the scientific literature regarding the role of exercise during treatment for breast cancer and this chapter seeks to summarise this evidence to date.
The question of whether exercise should be offered, or recommended, to women who are undergoing adjuvant treatment for breast cancer was addressed in a recent Cochrane Library systematic review [21]. This review was conducted in cooperation with the Cochrane Breast Cancer Group and followed the rigorous review methodology of the Cochrane Collaboration. Systematic reviews identify, appraise and synthesise research evidence from individual controlled trials and seek to form a robust basis for evidence-informed health policy and clinical decision-making. For this chapter the previously published Cochrane review was updated and included trials that post-dated the review. Consequently, for some outcomes the results may be slightly different from those reported in the Cochrane Review. Additional outcomes are included in this chapter that were not included in the Cochrane review, for example, bone health.

3.2.1 Methods of the Systematic Review

All methods of the systematic review (i.e. study selection criteria, study quality assessment, methods of data extraction and data analyses) were pre-defined in the review protocol. Study identification was based on a comprehensive search strategy with a variety of commonly used electronic databases and manual search methods.

Inclusion and exclusion criteria were developed in accordance with the review question; namely, should women undergoing adjuvant treatment for breast cancer be offered, or encouraged to exercise? These criteria were defined in terms of the population, interventions, outcomes and the study designs of interest. Only studies that met the inclusion criteria were included in the review.

Trials were included that reported on women receiving adjuvant treatment (chemotherapy, hormonal therapy or radiation therapy) for breast cancer. Breast cancer was restricted to stages 0–III. Trials which included women with stage IV breast cancer (i.e. with distant metastasis) were excluded from the review. Trials that included women who had completed adjuvant cancer treatment or who were being treated for other cancers were excluded. Trials with an intervention consisting of aerobic or resistance exercise were included, but those that examined complex exercise interventions (e.g. a programme of exercise and diet, or a programme of exercise and behavioural therapy) were excluded. Trials in which exercise interventions were restricted to selected body functions only (e.g. arm mobility) were also excluded. Trials were included that employed at least one of the following outcome measures: physical functioning, health-related physical fitness, symptom experience, biological or physiological outcomes, mental health, health-related QoL and adverse events. Randomised controlled trials (RCTs) and non-randomised controlled trials were eligible for inclusion in the review. No language restrictions were applied.

All studies were critically and systematically evaluated regarding their methodological quality (i.e. design, implementation and analysis) to determine the extent to
which the results were reliable. The exercise intervention was evaluated separately regarding its potential to provide an adequate training stimulus. Assessed components of the intervention included exercise intensity, exercise frequency, duration of single exercise sessions and duration of the intervention programme. Analysis of the training stimulus broadly followed current guidelines for exercise prescription for the elderly. Study selection, data extraction and critical appraisal of included trials were performed independently by two reviewers. Data from included trials were then combined using meta-analysis; this is a statistical procedure that integrates the results of several independent studies to give one overall estimate of intervention effects. A random effects model was chosen for the meta-analysis since heterogeneity between trials was expected.

### 3.2.2 Description of Studies

Fifteen studies that had assessed the effects of aerobic or resistance exercise training (or both) on physical and mental health outcomes in women during adjuvant treatment for early breast cancer were included in the review. The results were based on 1,042 participants from these 15 included studies. These studies were predominantly performed in North America (United States and Canada); only two of these trials [22, 23], a pilot study followed by a subsequent RCT were implemented in Europe from a single study group in the United Kingdom (Scotland). Sample sizes across trials ranged from 10 to 242 participants; only recently have large-scale trials of 100 participants or more emerged in the literature [23–26], with two [23, 24] of these including more than 200 participants.

Modes of adjuvant treatment were heterogeneous and varied across trials. Some trials included women who all received the same treatment mode, and others included women under different treatment regimens where participants were receiving chemotherapy and RT. Exercise interventions across studies were also heterogeneous. All the trials employed moderate intensity exercise interventions but differed in terms of setting, mode of exercise and programme duration. Settings included community-based exercise classes, fitness centre exercise and home-based exercise programmes. The mode of exercise differed across trials with some testing aerobic exercise interventions using walking, cycle ergometer training, treadmill and elliptical exercise machines and others evaluating combined aerobic-resistance exercise programmes. Two studies [24, 27] assessed the effects of an isolated resistance training programme. The exercise intervention periods in the included trials lasted from 6 weeks to 6 months. Trials with shorter intervention periods (less than 8 weeks) were focused on breast cancer patients receiving RT. Only two studies [22, 23], both performed in the UK, reported that the intervention was led by a model of behaviour change aimed at promoting adherence to a physically active lifestyle.

Multiple outcomes were assessed across studies. Apart from two trials [28, 29], all measured physical fitness, predominantly using cardiorespiratory fitness assessments and also through strength and body composition measures (i.e. weight, body
mass index, or lean body mass). Physical fitness measures are important indicators of physiological improvements gained through regular exercise but effects on physical functioning are also important, particularly in this population because this influences the ability to achieve and maintain an independent living status. However, physical functioning was only assessed in three trials [25, 26, 30].

Physical health was further assessed through biological and physiological outcomes and treatment-related symptoms. BMD was assessed in one study [27] and biological markers of immune system function or hormonal regulation in two studies [28, 31]. CRF was evaluated in nine studies [22–25, 28, 30–33] and several studies measured emotional distress through mood [31, 34], anxiety [24, 33] and depression [23, 24, 28, 33]. Self-efficacy [30] and self-esteem [24] were measured in one trial. Potential adverse effects, in terms of lymphedema, were also included as an outcome in one trial [24].

3.2.3 Effects

Findings from the systematic review and meta-analysis are presented in the following paragraphs. Data are reported in terms of ES (SMD) and 95% CI. SMD was used as the summary statistics for the meta-analysis because different assessment instruments measuring the same construct were used across studies (for example, for fatigue and body composition outcomes). The SMD can serve as a measure of strength of evidence but has limited value as a clinically meaningful measure of intervention effect. In the context of the meta-analysis, the interpretation of an effect as small, medium or large was based on an operational definition with conventional criteria: an ES of 0.2–0.3 was regarded as a ‘small’ effect, 0.5–0.7 a ‘medium’ effect and 0.8–1.0 as a ‘large’ effect. Exercise studies that provided adequate data for being included in the meta-analyses were of moderate and high methodological quality; one of these studies was a non-randomised study [33] but the results were similar to those of randomised trials.

3.2.3.1 Physical and Mental Health

Self-reported physical functioning was measured in three studies [25, 26, 30] but a meta-analysis for this outcome was not performed due to limited available data. Consequently, this review is unable to make any conclusions about the impact of exercise on self-reported physical functioning.

With respect to health-related physical fitness, meta-analyses were performed for cardiorespiratory fitness, muscular fitness and body composition. Exercise was shown to be an effective intervention for improving cardiorespiratory fitness in comparison to usual care (SMD: 0.54; 95% CI, 0.32–0.77), even during breast cancer treatment. This moderate effect was based on the results from eight studies with a total of 709 participants. Preserving cardiorespiratory fitness during breast cancer treatment is important, because vital aspects of physical functioning require
cardiorespiratory fitness. Pooling the data from four studies, with a total of 328 participants also yielded a moderate ES for a statistically significant increase in strength observed in exercising participants, compared to controls (SMD: 0.42; 95% CI, 0.06–0.78). There were, however, some inconsistencies in results across studies, which can be attributed to measuring strength after both aerobic and resistance training; typically, only resistance training is designed to increase muscular strength and power. Body composition outcomes, which describe the relative amounts of fat and lean tissue [35], were pooled from four trials (n = 414). Exercise was more effective than usual care in preventing unfavourable changes in body composition (SMD: –0.29; 95% CI, –0.55 to –0.03). Body composition is an important outcome, as overweight or obesity is associated with poorer prognosis in breast cancer patients [3, 36].

Regarding treatment-related symptoms, a meta-analysis for fatigue was undertaken. Pooling the data from seven studies (n = 714) that provided adequate data for fatigue showed that exercise was more effective than usual care in reducing feelings of fatigue (SMD: –0.17; 95% CI, –0.32 to –0.02), with the SMD indicating a small ES.

Bone health (BMD) was the primary outcome measure in one trial [27] which reported that aerobic exercise preserved lumbar spine BMD better than usual care alone. Bone health is a particularly relevant outcome measure for women who have had breast cancer because they are at higher risk for osteoporosis and subsequent osteoporotic fractures than other women [3, 37, 38]. Furthermore, as many women with breast cancer will be long-term survivors, the importance of skeletal health should not be underestimated, moreover, it should be actively promoted in this population of women.

For mental health outcomes, the ESs were small. Pooling the effects of three trials yielded a reduction in cancer-related depression in the exercise groups compared to controls (n = 443) (SMD: –0.24; 95% CI, –0.43 to –0.04). Results for anxiety suggested a small, but non-significant effect of exercise (n = 269) (SMD: –0.25; 95% CI, –0.54 to 0.04) from two studies.

3.2.3.2 Adverse Events

In this patient group, consideration of the adverse events during interventions is important for weighing up the benefits and risks of exercise in clinical decision-making. Although beneficial, exercise may also increase the risk of injury and women receiving adjuvant treatment for breast cancer might be more vulnerable to such risks in comparison to healthy women. For example, participants may be at increased risk of exercise-related traumatic or overuse injuries. Minor musculoskeletal injuries such as sprains, strains, joint pain and overuse injuries could be anticipated in sedentary people who begin an exercise programme. Additionally, musculoskeletal risk is likely to be higher for older breast cancer patients due to the age-related decline in physical fitness, loss of skeletal muscle mass and decreased bone density, which can be further exacerbated by breast cancer and treatment modalities. There may also be concerns that PA could exacerbate arm lymphedema,
a common side effect of breast cancer therapy, which can result in substantial functional impairment. Finally, previously sedentary middle-aged and older women who are treated with cardiotoxic drugs may be at increased risk of an adverse CV event occurring during or following an acute bout of physical exercise.

The potential adverse events of exercise during breast cancer treatment have generally been disregarded in the literature. When adverse events have been recorded, they have been spontaneously reported by participants, rather than by AS (where participants are asked about the occurrence of specific adverse events in structured questionnaires or interviews, or pre-defined diagnostic tests are performed at pre-specified time intervals). Spontaneous reports typically result in fewer recorded incidents/occurrences than AS [39].

Passive surveillance of adverse events across studies included in the review did not reveal any increase in injury rates or other adverse events in the exercise groups compared to non-exercising control groups. No single study performed AS of injuries occurring in exercise interventions during adjuvant treatment for breast cancer. However, of some relevance here is that active injury surveillance undertaken in exercise studies after adjuvant treatment for breast cancer has indicated that weight training is well tolerated, with rates of minor injuries comparable to those observed in the general population [40]. Only one study actively surveyed for lymphedema [24], with no increased risk associated with exercise during adjuvant treatment for breast cancer [24].

In summary, the present available evidence regarding safety of exercise during adjuvant breast cancer treatment is limited. The safety concerns described in this section are highly relevant to exercise promotion in the period of adjuvant cancer treatment because uncertainty about the safety of engaging in exercise may act as a barrier to adopting a physically active lifestyle in this population. Similarly, physicians who are reluctant to prescribe exercise are likely to be influenced by this evidence gap regarding safety, despite the growing body of evidence which supports the benefits of moderate intensity exercise during breast cancer treatment. It is also possible that regular exercisers could be discouraged from being physically active during and after breast cancer treatment by doctors, other health professionals and their families. Therefore, safety needs to be systematically addressed in future exercise studies.

### 3.2.4 Exercise Adherence and Maintenance

Measuring adherence to exercise in trials is important because the failure of participants to adhere to exercise prescriptions may bias the findings, hence limiting the strength of the evidence generated. Exercise adherence refers to the level of exercise participation achieved once the individual has decided to follow an exercise training programme. There are two components of adherence: attendance at exercise sessions and the exercise intensity achieved when compared with the target intensity (as prescribed).
In general, exercise adherence can be calculated by comparing actual exercise behaviours with the standards determined in the exercise recommendation. Different approaches were used among the included studies to measuring adherence: the ratio of attendance to scheduled exercise sessions and the proportion of adherent participants with various cut-points of exercise per week. Adherence to exercise was said to be 70% or more of possible exercise sessions in seven studies [22, 24, 26, 30–32, 41] and may have been of similar magnitude in a further study [42], as participants were allowed to repeat missed sessions. In another study [23], less than 40% (38.8%) of participants achieved at least 70% of the available exercise sessions. In studies that assessed proportions of adherent participants, these were 72% [25] and 86% [33] based on cut-points of 60 and 90 min of exercise per week, respectively. No information on adherence to the prescribed exercise was given in four trials [27–29, 34]. It should be noted that attendance rates are difficult to compare, across studies because different exercise stimuli are prescribed and various cut-off points used for determining rates of adherent participants.

Additional information on adherence can be gained by examining participant behaviour during prescribed exercise sessions. Two of the included trials reported exercise adherence in terms of exercise intensity and duration [24, 41]. The aerobic exercise training group in one of these studies met their prescribed duration 96% of the time and intensity 87% of the time [24]. In the other study [41], an average exercise duration of 43 min, with an average duration of exercise within prescribed target heart rate zones of 28 min, was reported.

Data on exercise participation in non-exercising control groups (contamination) were reported in three trials [24, 25, 30]. The percentage of participants in the control group that reported regular exercise outside of the study was less than 15% in one study [24] but reached 39% in another study [25].

A major challenge for health-related lifestyle change is not the initial change but rather the ability of participants to adhere to a change in the long term. Maintaining exercise beyond an intervention (i.e. long-term adherence to exercise) is a critical concern because the benefits of exercise may not persist when exercise is discontinued. It can be assumed that sustained exercise participation is required to experience long-term benefits in both physical and mental health outcomes. In the case of depressive symptoms, for example, regardless of whether the mechanism of action is based on distraction, social involvement during exercise sessions or physiological pathways such as endorphin secretion, the underpinning mechanism has to be stimulated.

Conflicting evidence exists for the impact of exercise interventions on long-term adherence. Six-month follow-up data from one study [43] suggested that a supervised exercise training programme during adjuvant chemotherapy is an effective strategy for helping sedentary breast cancer patients to move towards a physically active lifestyle, but data from a second study [23] showed a decrease in the PA levels of the exercise group between the end of the intervention period and the final assessment.

Understanding the ways in which individuals sustain healthier long-term lifestyle choices is needed to help cancer patients maintain recommended levels of physical
activity. Knowing the key barriers women face when receiving adjuvant treatment for breast cancer may serve as a basis for the development of interventions to assist women in exercising regularly during this difficult time. Several studies have investigated predictors of adherence to exercise in women but these have mainly recruited young healthy women. Predictors of exercise adherence in younger healthy adults may be quite different to those for elderly populations of women with breast cancer. The identification of reliable predictors of exercise adherence will allow health-care providers to effectively intervene and support sedentary women during the process of changing their patterns of PA. Many barriers (real or perceived) exist, which represent obstacles to maintaining regular exercise in the period of cancer treatment. In this respect, the assessment of barriers to supervised exercise in breast cancer patients participating in a randomised controlled trial [44] showed the importance of disease- and treatment-related barriers; feeling sick, fatigue, chemotherapy day, nausea/vomiting and depression, amongst others, accounted for more than half of the missed sessions among breast cancer patients.

Issues related to gender also appear to be important barriers to exercise participation. A focus-group study [45] of the experiences of women with breast cancer who took part in an exercise trial suggested that the woman’s traditional role as a caregiver and concerns about body image act as potential barriers to PA and that a gender-sensitive approach may help overcoming barriers to PA, e.g. exercise classes solely for women with breast cancer provided within a supportive group environment. Addressing barriers, particularly disease and gender-related barriers, is a critical issue that will impact upon exercise adherence during treatment for breast cancer.

3.2.5 Quality of the Evidence

Since the earliest exercise intervention studies during adjuvant therapy for breast cancer, the field has grown and the methodological rigour of studies has improved. Recent studies have tended to include larger samples sizes, sometimes with about 100 participants per group and have performed statistical power calculations to estimate the required sample size. This is important because the benefits of exercise may be relatively small and without an appropriate sample size, studies may be underpowered to detect such effects. Thus, the sample size should be great enough to allow the detection of small differences between groups, if they exist. Also, reporting of the trial methodology has improved in recent years and most now adhere to the CONSORT Statement guidelines in relation to the reporting of trial design and data analyses. Key methodological limitations of studies included in the review were observer blinding, concealment of intervention allocation and lack of intention-to-treat analysis. Moreover, there were inconsistencies in results between trials and wide CI were observed for several findings.
3.2.6 Applicability of the Evidence to the Breast Cancer Population

Considering that in the USA the median age of women at breast cancer diagnosis is 61 [46], the women included in the primary studies of the meta-analysis were relatively young, with a mean age of 50 years. Hence, a major shortfall of the available evidence is the severe lack of studies which have focused on older women. Applying the findings from this review to older women could be problematic for a number of reasons. For example, it is not known whether older breast cancer patients derive similar benefits from exercise or whether they are more vulnerable to injury. Also, exercise participation rates and adherence are unlikely to be comparable to those of younger women. The determinants of exercise motivation and exercise behaviour may also differ. One recent pilot study [28] has focused on older women (mean age of 65 years) but this group still remains and understudied population.

3.2.7 Implications for Research

There is a need for further research (including studies with adequate statistical power) which is focused on the effects of exercise therapy in women receiving adjuvant treatment of breast cancer to develop the evidence base. Achieving a consensus among researchers on outcome measures to be included in exercise studies is also needed to assist the interpretation and comparison of results. The long-term follow-up of exercise interventions requires more attention because some side effects of adjuvant cancer treatment are either long term (e.g. fatigue and deconditioning) or may influence recurrence and mortality (e.g. weight gain). In addition to health-related outcomes, adherence and contamination, adverse events should be systematically assessed and reported as well. In efficacy trials, investigators need to ensure that participants adhere to the intervention to establish whether exercise interventions in this population work. The inclusion of only sedentary participants could help to deal with contamination issues as sedentary women might be less likely to start their own exercise programme in the period of adjuvant cancer treatment. In effectiveness trials, both adherence and contamination should be reported as an outcome measure because poor adherence can render an efficacious intervention as ineffective.

Given the known functional decline, especially in older women receiving adjuvant treatment of cancer, physical function becomes an important outcome. Physical function assessments may include objective measures of mobility, as well as self-reports of mobility and lifestyle activities. Since older women are still an understudied patient population, the age group of women older than 60 years should be a particular feature of future research.

Future research also needs to investigate how individuals sustain long-term healthy lifestyle choices, such as maintenance of a physically active lifestyle. Exercise adherence during cancer treatment constitutes a challenge and thus,
programmes are needed to facilitate exercise participation while helping to overcome barriers to change. For behaviour changes to occur (the adoption of regular exercise in this instance) it is important that intervention programmes focus on the underlying principles of behaviour change theories.

Enjoyment is an important component of compliance to exercise interventions. Diversity of options, with a mixture of traditional forms of exercise and more novel forms of exercise, such as pilates and Nordic walking and dancing, may result in greater enjoyment, once adequately adjusted to the individuals’ needs and the limitations of this population of women. In addition, partner-assisted exercises may also promote exercise enjoyment. Barriers to exercise that are related to time management may be addressed by the provision of exercise classes in different locations. Choosing venues that are accessible by public transport and by timetabling classes at various times in the day and evening may also prove useful.

Finally, more attention needs to be focused on identifying cost-effective ways to expose patients to exercise participation, outside university or cancer centres but within local communities.

3.3 Implementation and Dissemination

The benefit of any exercise intervention is determined not only by its efficacy, but also by the extent to which it is appropriately adopted and implemented in the community. The exercise rehabilitation programmes established in Germany for women who have been treated for breast cancer (breast cancer survivors) are an example of how exercise could be offered to breast cancer patients during treatment within a health-care context. Currently, more than 600 rehabilitation sports groups exist in Germany, providing exercise classes for breast cancer survivors within the framework of organised sports. A particular strength of these groups is that they are local, thus allowing participation in structured exercise programmes in the vicinity of participants’ homes, a model which could easily be adapted for women undergoing treatment for breast cancer.

Already in 1991, a training curriculum for exercise facilitators was established in Germany and since 1992, exercise for breast cancer patients has been included in the German Sports Federation guidelines for exercise facilitator training [47]. The legal foundations for exercise rehabilitation programmes are contained in Book 9 of the German social code, SGB IX (covering rehabilitation and participation of people with disabilities). According to SGB IX, exercise rehabilitation programmes are to be provided and funded as supplementary benefits to rehabilitation. Rehabilitation sports groups for breast cancer patients are formally prescribed by the treating physician and led by qualified instructors (Übungsleiter/innen) to ensure competent and skilful guidance and surveillance of classes. However, a physician is always on hand to counsel participants and the exercise facilitators when required. The cost of participation in these programmes is reimbursed to sports clubs by health or retirement insurance funds.
3.4 Summary

In summary, physical exercise appears to be an effective intervention for improving important health outcomes during breast cancer treatment. There is evidence for a moderate effect of exercise on cardiorespiratory fitness, muscular fitness and body composition, and for a small positive effect of exercise on fatigue. Evidence is limited regarding a positive effect of exercise on anxiety and depressive symptoms. Evidence of adverse events resulting from exercise rehabilitation during this vulnerable period of breast cancer treatment is sub-optimal because most studies have not addressed this issue systematically. Although there is currently no evidence that women undergoing breast cancer treatment who engage in exercise programmes are at an increased risk for injuries, lymphedema or other adverse events, this issue needs to be given more attention in future studies. Further research also needs to focus on older breast cancer patients to improve the ecological validity of the evidence base. Finally, the implementation of exercise opportunities for cancer patients, such as those endorsed by the national sports federation in Germany, may offer a framework or working model that could be adopted by other countries.

References

Chapter 4
Exercise After Treatment for Breast Cancer: Effects on Quality of Life

Helen Crank and Amanda Daley

Abstract  Whilst the incidence of breast cancer is high, survival is good and has improved significantly over the past 30 years. A diagnosis of breast cancer can be a life-changing event for women and treatment can be intense and prolonged; this can have a detrimental effect on QoL. Exercise may be a means by which the QoL of cancer survivors can be improved. Evidence from numerous trials have shown that many of the physical, functional and emotional effects that are typically experienced by women after treatment for breast cancer may be ameliorated, at least in the short term, through participation in regular exercise, regardless of mode or setting. However, despite considerable advancements in this field, we must remain cognizant that we have a long way to go and many questions remain unanswered. There is still a need for larger trials of high methodological quality that include long-term follow-up.

4.1 Introduction

4.1.1 Incidence and Survival from Breast Cancer

Breast cancer is by far the most common cancer in women [1, 2]. Whilst the incidence of breast cancer is high, survival is good and has improved significantly over the past 30 years [3]. The aging of the population coupled with substantial improvements in the early detection and treatment of cancer mean that the number of people treated successfully with cancer will continue to grow. The high incidence rate, in conjunction with the favourable survival rate, highlights that the quality of that survival is an important issue for patients, clinicians and researchers. The focus on recovery issues and adverse long-term consequences of treatment are clearly

H. Crank (✉)
Faculty of Health and Wellbeing, Centre for Sport and Exercise Science, Sheffield Hallam University, Sheffield, S10 2BP, UK
e-mail: h.crank@shu.ac.uk

important and rehabilitation from cancer treatment is increasingly being recognised as a chronic medical condition necessitating management over the long term [4].

4.1.2 Consequences of Breast Cancer

A diagnosis of breast cancer can be a catastrophic life event for women and treatment can be intense and prolonged. A myriad of physical, functional and emotional effects can be experienced during and after treatment [5–7], and this can have detrimental effect on QoL. The physical side effects from treatments for breast cancer include fatigue and weight gain, asthenia, ataxia, lymphedema, reduced CV function, muscle weakness and atrophy. Other physical complaints reported by survivors of breast cancer include nausea, vomiting, pain, pre-mature menopause and hot flushes and osteoporosis [8–10]. Common psychological and emotional consequences of cancer diagnosis and treatment often include depression, anxiety, stress, decreased self-esteem, body image concerns, social isolation, loss of sense of control and the fear of cancer recurrence [11–13]. The psychological responses often associated with breast cancer are of concern in themselves, but are also likely to impinge upon survivors’ health behaviours [14, 15] that could have consequences for QoL. It is therefore critical to assess the merits of treatments that may improve the QoL of this population and enhance recovery following treatment for breast cancer.

4.1.3 Psychological and Psychosocial Interventions

Numerous psychological interventions (e.g. psychotherapy and support groups) are available to assist patients in recovering from cancer diagnosis and treatment, but these interventions report relatively small ESs [16], highlighting the need for alternative treatments. A common feature of current psychosocial interventions is that they focus largely on psychological issues and are less likely to address adequately the physical and functional problems that breast cancer survivors face. This issue is important because physical and/or functional problems may, at least partially, be responsible for the psychological morbidity experienced by patients after treatment(s) for cancer [17]. Maximising the physical and psychological functions that are affected by the disease and treatment(s) is clearly pivotal to the restoration and potential enhancement of cancer survivors’ QoL; exercise may be a means by which both of these functions can be improved.

4.2 The Potential Role of Exercise After Treatment for Breast Cancer

There is already good evidence that regular exercise has positive effects upon many of the symptoms and chronic impairments that are associated with treatment for breast cancer; examples include depression, self-esteem, insomnia, anxiety, fatigue,
muscle strength, weight maintenance, osteoporosis and atherosclerosis [18–23]. This poses the question of whether exercise can be an effective therapeutic QoL intervention for women recovering from breast cancer treatment. Exercise could have the potential to provide health benefits to this population of women at a time in their lives when their risk of many other chronic diseases is increased. Because of this increased risk, it may be more important for survivors to participate in regular exercise than might be the case for the general population. Indeed, similar to the general population, very few cancer survivors are achieving recommended levels of PA [24]. Specifically, breast cancer survivors have been found to have low levels of PA, which often remains low for many years after treatment is completed [25, 26], resulting in further de-conditioning and CV function, as well as changes in weight status and body composition [27, 28].

4.3 Chapter Overview

Exercise may have benefits throughout the spectrum of the cancer experience, but we focus here on providing a succinct overview of the evidence regarding the efficacy and effectiveness of interventions for improving QoL specifically in breast cancer survivors. Evidence has been summarised from studies located through electronic searches, as well as references cited in other reviews. Given the potentially broad nature of ‘QoL’ and the extensive literature base, we have focussed primarily on reviewing studies that are randomised controlled trials (RCTs) and/or have made a significant contribution to advancing knowledge in the field. We also present a brief overview of relevant systematic reviews and meta-analyses. A number of qualitative studies have explored breast cancer patients and survivors’ experiences of participating in exercise programmes and we provide a summary of these studies here. Some researchers refer to their intervention(s) as ‘PA’ whilst others use the term ‘exercise’; where appropriate we have described studies according to whichever term the study authors used.

4.4 Is Exercise an Effective Quality of Life Intervention After Treatment for Breast Cancer? Summary of the Evidence

In the following sections we have attempted to provide an historical overview of some of the important studies that have taken place over the past 20 years and draw attention to the methodological shortcomings of previous studies, which need to be addressed by future research. Our aim is not to provide an exhaustive list of studies but to provide a taste of work to date. We have also used particular studies as vehicles for raising pertinent issues that we felt were worthy of discussion. By drawing together this information here we hope to guide researchers, health professionals and health policy makers towards a more complete understanding of the evidence surrounding the effects of exercise on QoL in breast cancer survivors.
4.4.1 Setting the Scene: Early Intervention Studies

The pioneering work of Maryl Winningham was pivotal in progressing knowledge in this field during the 1980s. This research [29–32] showed that exercise training performed during treatment had the potential to improve the health of cancer patients. Despite having small sample sizes, these early studies offered research groups a platform on which to investigate in earnest the potential effects of different types of exercise/PA interventions for breast cancer survivors, as well as other cancer populations.

4.4.2 The ‘Boom’ Years

The next decade saw a global expansion in the number and diversity of intervention studies taking place. Research groups established across six continents undertook multiple studies investigating the effect of different modes of exercise on a host of physiological and psychosocial outcomes. The ensuing clinical and methodological diversity of trials has often made it difficult to draw comparisons between trials and this is most apparent in systematic reviews and meta-analyses. In order to provide a general framework for understanding the evidence published during the ‘boom years’, we have loosely categorised studies into sections according to the type of exercise/PA intervention(s) evaluated, although this is not straightforward because of the varied nature of studies and because some studies might naturally fall into more than one category. We have also included some discussion of the merits of exercise/PA interventions relative to other traditional QoL interventions used with cancer survivors.

4.4.2.1 Trials of Supervised Aerobic Exercise

An early pilot RCT [33] that recruited 24 breast cancer survivors (diagnosed in previous 3 years) found that participants in a 12-week supervised aerobic exercise intervention reported significantly higher body esteem scores compared to a wait list control group, but did not report improvements in feelings of sexual attractiveness, mood states or positive and negative affect scores. The small sample size, coupled with the drop out from both groups, is likely to have reduced the statistical power of the study to detect group differences in these outcomes however. Using within group analyses improvements in blood pressure and sub-maximal heart rate were seen in the exercise group. Adherence to the intervention was high at 88%, indicating that this population can tolerate the demands of a progressive aerobic exercise programme.

A larger RCT (n = 53) [34] examined the effects of supervised aerobic exercise on health outcomes relative to a wait list control in breast cancer survivors. The intervention had significant beneficial effects on cardiopulmonary function and QoL. Improvements in cardiopulmonary function were also associated with improvements in QoL and on this basis the trial authors suggested that aerobic exercise
interventions should be designed to induce cardiopulmonary adaptations. The trial recorded high adherence (98.4%) but a very low recruitment rate (14%); high adherence coupled with a low recruitment rate can be a concern because it may indicate that atypical highly motivated participants have been recruited, limiting generalisability. Similar to many other previous studies, this trial did not include follow-up beyond the end of the intervention, so we have no indication of the longer term benefits that the intervention might provide, if any.

A question that has been raised many times in the literature is the issue of whether improvements in QoL are the consequence of the increased attention given to participants involved in exercise interventions. In response to calls [33, 35] for researchers to design exercise trials that control for possible attention effects arising from instructor–patient interaction, in one of our own trials [36, 37] (SHERBERT) we randomised breast cancer survivors to individualised supervised aerobic exercise therapy, equal contact attention control (light body conditioning exercises) or usual care over 8 weeks (n = 108). Aerobic exercise therapy had large clinically meaningful beneficial effects on QoL at the end of the intervention, which could not be attributed to attention as the equal contact control group did not report similar effects relative to usual care. Additional follow-up at 24 weeks from baseline was also included but effects for QoL were not maintained. Of interest here, depression scores were significantly lower in the aerobic exercise therapy and the attention control groups, compared with usual care at both follow-ups and only a small benefit for depression beyond the effects of the attention was shown. These findings might indicate that attention effects, at least in part, may be responsible for some of the psychological benefits experienced by cancer patients who engage in exercise programs and reinforce the need for attention control groups in trials when assessing psychological outcomes. As reported in other trials [34], the recruitment rate of eligible patients in SHERBERT was modest at 29%, which may raise further concerns about the general viability of supervised exercise programmes for cancer survivors.

The YES trial [38] randomised breast cancer survivors (n = 75) (diagnosed 1–10 years previously and completed adjuvant treatment 6 months prior to study entry) to exercise or usual care groups over 6 months. The YES intervention involved predominantly supervised group-based aerobic exercise training, 3 times.week⁻¹ at a health club. Participants were also encouraged to exercise for two further sessions per week, either at home or at the health club. On average, over the course of the intervention the exercise group increased their participation in moderate-to-vigorous intensity by 129 min.week⁻¹, compared with 44 min for usual care. Whilst the sample size in the YES trial was modest, it is nonetheless notable because the intervention lasted 6 months, one of the longest to date and because it included follow-up 18 months after randomisation to provide much needed information on maintenance issues (data not currently available). Despite extensive efforts, however, the trial was only able to obtain an accrual rate of 9.5%.

To conclude, evidence suggests that, at least in the short term, supervised aerobic exercise interventions can improve QoL in breast cancer survivors, regardless of whether exercise occurs on an individual or group basis. Group-based exercise
programmes may provide added value over individual ones by providing an element of social support to participants, which may be particularly important to cancer survivors. The strength of supervised programmes is that they provide the opportunity to monitor precisely patients’ progress, many of whom will have previously been inactive for sometime, and may require support and encouragement as they begin to integrate PA into their lives after cancer treatment. However, supervised programmes are not without drawbacks and can pose substantial feasibility concerns in terms of costs and accessibility, as clearly demonstrated by the low recruitment and accrual rates in the trials reviewed here. Moreover, given the high survival rates for many cancers, particularly breast cancer, it is unlikely that health-care providers would have the financial resources to be able to offer supervised exercise programmes and facilities to all survivors of cancer. Indeed, whether such interventions are cost-effective is not known and this must be a high priority for future research.

4.4.2.2 Weight Training and Resistance-Based Exercise Interventions

Resistance exercise has been advocated for general populations of women, particularly those who are post-menopausal, because of the beneficial impact on muscle strength, functional capacity and risk of osteoporosis [39, 40]. A high proportion of women will experience reductions in their functional capacity after treatment and many of the therapies used in breast cancer are associated with bone loss (particularly those that induce a therapeutic pre-mature menopause or lower post-menopausal oestrogen concentrations), which in turn may lead to an increased risk of fractures [41, 42]. With these issues in mind, attention has begun to focus upon understanding the safety and efficacy of resistance-based exercise for women who have undergone treatment for breast cancer. Whether resistance training can improve other related QoL outcomes such as depression, self-esteem and body image and lymphedema in these women has also been of interest to researchers in recent years.

The WTBS study [43] compared the effects of a 6-month weight training intervention (combination of supervised and unsupervised) with no intervention (control) on a range of physical and psychological health outcomes \( n = 86 \). The trial included partial crossover between months 7 and 12 where the exercise group continued exercising and the control group also participated in the same exercise intervention. We focus here on findings prior to crossover. The intervention had significant beneficial effects on physical global and psychosocial QoL, but not depression, at 6-month follow-up. In addition, of interest here are the findings that improvements in QoL were associated with increased lean muscle mass and upper body strength, suggesting that QoL changes from participation in weight training exercise might be mediated via these outcomes. Depression scores did not reduce significantly as a result of the intervention, but only about 12% of participants were depressed at baseline so the trial had limited scope to impact upon this outcome.

Lymphedema remains a common problem for women after treatment for breast cancer, with prevalence reported to be in the region of 28% [44], and current treatments do not offer a permanent reduction to arm swelling [45]. There appears
to be some reluctance by clinicians to recommend exercise to women who have
developed lymphedema after cancer treatment because of fears that it will exac-
terbrate the symptoms. It is encouraging to see that a further publication from the
WBTS trial [46] found no change in arm circumference and the incidence of lym-
phedema or symptom changes over the course of the intervention did not differ
by group. Another publication from the WBTS trial [47] that reports on other
outcomes such as body composition, IGF peptides is also available to interested
readers.

WTBS did not include any bone health outcomes but given that studies involving
general populations have shown positive effects on bone health from participation in
resistance exercise, it could be reasonably expected that similar results would ensue
for breast cancer survivors, who are at high risk for this condition. A number of
trials that are examining these questions are underway so we may have more direct
evidence regarding this question in due course.

Publications from the WTBS contribute to the growing evidence that weight
training resistance exercise is not only safe, but can also facilitate psychosocial and
physical well-being changes that aid recovery from breast cancer treatment. Weight
training or resistance exercise may help breast cancer survivors to ‘feel strong’ and
empower them with feelings of physical competence; this may then manifest in
enhanced QoL and feelings of well-being. Whilst additional follow-up beyond the
end of the intervention was included in the WTBS trial, the use of a crossover design,
coupled with a small sample size, makes it difficult to interpret these data. However,
the inclusion of a 6-month intervention is a notable methodological strength of this
trial. The findings from ongoing trials of resistance training may shed further light
on the potential contribution that this mode of exercise can have on the health and
well-being of women who have been treated for breast cancer. In the meantime,
findings from the WTBS trial are encouraging.

4.4.2.3 Combined Aerobic Exercise and Resistance Training Interventions

Several RCTs have evaluated the efficacy of combined aerobic and resistance exer-
cise on the premise that exposing participants to both types of exercise could provide
greater QoL benefits than either type alone. In an early RCT [48], the effects of a
combined supervised progressive weight training and aerobic exercise intervention
were compared with a non-exercise control group over 8 weeks in breast can-
cer survivors (n = 12). The exercise group significantly improved their physical
functioning (assessed by a walk test) relative to controls. Early-stage breast cancer
survivors (n = 14) with unilateral, upper extremity lymphedema were allocated to
an 8-week upper body aerobic and ergometry exercise programme or a no-exercise
group [49]. Similar to findings from the WBTS trial [46], no changes in arm cir-
cumference or arm volume in the combined exercise group were found and QoL
significantly improved in the exercise group compared to controls. While the sample
size in the McKenzie and Kalda trial [49] was very small, it provides further evi-
dence to challenge the perception that exercise may lead to, or worsen, lymphedema.
Other QoL benefits from a combined aerobic and resistance exercise intervention
were reported in another pilot RCT \( (n = 16) \) in which QoL, aerobic fitness, leg press and sit-to-stand test scores improved significantly in the intervention group, compared to control [50].

More recently Milne et al. [51] investigated the effects of 12-week combined aerobic and resistance exercise intervention on QoL outcomes in a larger sample of 58 women who were within 2 years of diagnosis. Participants were randomised to an immediate exercise or a delayed exercise group, with complete crossover. The immediate exercise group reported significantly higher QoL, fatigue and social physique anxiety scores than the delayed group at the end of the 12-week intervention. The magnitude of the effect for QoL outcomes was particularly noteworthy and findings for breast cancer-specific QoL far exceeded the minimal clinically important difference for the scale [52]. Additional follow-up in the trial was reported at 18 and 24 weeks from baseline, but again the use of a crossover design makes it difficult to interpret these data. It also seems important to highlight here that adherence to the intervention was about 60\%, much lower than reported in trials that have used single-component exercise interventions [34, 37]. A further publication from the trial reported that the intervention had a positive impact on the psychological needs and motivational variables of self-determination theory [53].

Taken together these findings suggest that multi-component exercise interventions may make a substantial difference to the health of women who have been treated for breast cancer. That said, some caution is required when interpreting the findings from these trials because they typically include small or modest sample sizes, so bias could be present. Furthermore, the low adherence level found in the Milne et al. trial [51] should not be ignored and researchers and practitioners may want to give this issue due consideration when selecting and planning future interventions.

### 4.4.2.4 Pragmatic Home-Based Exercise Interventions

As stated previously, supervised programmes tend to have high running costs and typically require a facility, equipment and an instructor. In addition, supervised programmes often mean that participants have to travel to a centre, which may prove difficult for some women who have to juggle family and employment responsibilities. Indeed, there is evidence that transportation issues are by far the most common reason why breast cancer patients and survivors decline to participate in supervised exercise trials [38, 54]. Given these barriers, research has begun to move away from evaluating supervised facility-based exercise interventions, towards assessing the relative merits of pragmatic community-based approaches.

The Moving Forward RCT [55] examined whether sedentary early-stage breast cancer survivors \( (n = 86) \) could adopt a home-based PA program delivered by telephone over 12 weeks. As hypothesised, the PA group reported more minutes of moderate intensity PA and higher energy expenditure per week than controls. However, changes in self-reported PA were not reflected in the objective activity assessments (accelerometry). No significant differences were found in BMI or percentage body fat either, although weight loss was not the goal of the intervention.
Analyses also showed that the intervention group reported higher vigour and lower fatigue scores at follow-up, providing yet further evidence that ‘rest may not be best’ after treatment for breast cancer.

In Project LEAD [56], breast and prostate survivors aged over 65 years were randomised to a 6-month home-based exercise and diet intervention (delivered via tailored print material and bi-monthly telephone counselling) or an attention control group. Follow-up took place 6 and 12 months from baseline. Regrettably, the ambitious recruitment target of 420 participants was not met. Nevertheless, recruitment of 182 elderly cancer survivors is still a notable achievement. Based on those who were recruited, the majority being breast cancer survivors (n = 104), no significant group differences in physical functioning, PA energy expenditure or QoL were reported at 6-month follow-up, but scores did generally favour the intervention group. Self-efficacy for exercise and diet quality scores were significantly higher in the intervention group, relative to attention control at 6 months. Higher self-efficacy scores might indicate that the intervention was at least successful in promoting the belief in participants that they could achieve regular involvement in exercise. It is also interesting to note that differences between groups were diminished between the 6- and 12-month follow-ups, indicating that participants struggled to maintain their new lifestyle behaviours over time. The issue of how best to maintain changes in exercise behaviour is a topic of ongoing debate in the literature and it might be that patients, particularly those who are elderly, require ongoing prompts or support after the initial intensive phase of an intervention is completed. The recruitment difficulties experienced in Project LEAD are not uncommon and have been experienced by numerous other trials, highlighting the complexities involved in successfully completing exercise trials with cancer populations.

In a large well-conducted RCT (n = 377) by Vallance et al. [57, 58] breast cancer survivors were randomly assigned to one of four groups over 3 months. All participants received a standard PA prompt via telephone. In addition, three of the four groups received breast cancer-specific PA print materials, a step pedometer or both. Follow-up was completed 3 (end of the intervention) and 9 months after baseline. At 3 months, self-reported PA was increased across all four groups, with the greatest difference between the standard recommendation comparator and the step pedometer groups. There were no differences in objectively determined (pedometer) walking behaviour between the groups at 3 months. Furthermore, the combined print materials and step pedometer group reported significantly improved QoL and fatigue scores compared to the standard recommendation group. At 9 months from baseline, none of the three PA groups reported significantly more PA than the standard recommendation group, but the pattern of results was similar to those found at 3 months, demonstrating only a small reduction in the effect of the interventions over time. There were no significant differences in QoL or fatigue between groups at 9 months. The large sample size in this trial is a considerable advancement over previous studies and it is encouraging to see that large pragmatic PA trials involving cancer populations can recruit successfully.

Cancer physicians may serve as a powerful source of motivation by conveying the importance of a healthy lifestyle to patients during and after treatment for
cancer. Taking this on board, Jones et al. [59] compared the effects of a brief oncologist recommendation to exercise delivered during treatment consultations with and without additional support from an exercise specialist, with usual care, in newly diagnosed breast cancer patients \( (n = 450) \). Follow-up was short and took place 5-week post-treatment consultation. Findings showed that patients who received a prompt from their oncologist to exercise reported participating in significantly more exercise, relative to usual care at follow-up \( (10.1 \text{ vs. } 6.7 \text{ MET h.week}^{-1}) \). It is difficult to determine the clinical significance of these findings (difference of 3.4 MET h.week\(^{-1}\)), although evidence from observational studies suggests that even relatively small amounts of regular PA \( (\geq 3 \text{ MET h.week}^{-1}) \) may be positively associated with survival after breast cancer [60].

Findings underline the persuasive role that clinicians can have on cancer patients’ exercise behaviour and highlight the fact that changes to lifestyle can be achieved in cancer patients by adopting relatively simple interventions requiring little expertise to develop, effort to deliver or ongoing resources. No published RCT has considered the effects of prompts from oncologists on exercise behaviour and QoL, specifically in women who have completed treatment for breast cancer, although it is likely that Results from the Jones et al. trial [59] would generalise to survivors, who continue to see their oncologist in clinic for follow-up for many years after completing treatment. The role of cancer care clinicians in facilitating exercise behaviour change in survivors is certainly a question that researchers should pursue not least because these types of interventions are low cost and could be implemented into cancer care settings with relative ease, time permitting.

Previous trials have used research staff or health-care providers to deliver the interventions and one of the most recent developments in the field has been the use of volunteers, who themselves are cancer survivors, to promote PA with other cancer survivors. In a single group feasibility study [61], seven volunteers were trained to deliver a telephone-based PA intervention to survivors of breast cancer \( (n = 25) \). Volunteers delivered 12 weekly calls to encourage participation in moderate intensity PA. Follow-up of outcomes took place at 12 and 24 weeks from baseline. Levels of PA, as assessed by self-report and pedometers, increased significantly from baseline to post-intervention at 12 weeks, and improvements in fatigue, QoL and vigour were also found; these effects were maintained at 24 weeks of follow-up. The intervention was demonstrated to be feasible and acceptable to volunteers, with an average of 11 out of 12 calls delivered as intended and participants also rated the program very positively. These results appear very promising and the use of volunteers or ‘buddy’-based interventions may offer a sustainable method by which cancer survivors can receive long-term support that encourages regular PA, but this approach now needs to be evaluated in the context of an RCT.

Given the high incidence and improved survival rates for breast cancer, the focus should now be to evaluate ecological interventions that can be easily implemented into community and cancer care settings, so that the greatest number of cancer survivors can participate and experience the benefits that PA may offer. Collectively, studies have demonstrated that brief, low-cost exercise/PA interventions can be efficacious and that supervised facility-based interventions are not necessarily required
to increase PA behaviour and improve QoL in survivors. That said, we must be mindful that many studies may have recruited atypically motivated samples and follow-up has generally been short, so findings may represent the best case scenario. The critical question must now be to consider whether these approaches have the ability to facilitate sustainable changes in exercise behaviour and QoL in more representative samples of breast cancer survivors.

4.4.2.5 Alternative Modes of Exercise

In a departure from investigating the effects of ‘traditional’ types of PA a pilot RCT [62] of 21 women who had been treated for breast cancer explored the efficacy of a 12-week Tai Chi intervention compared to a supervised psychosocial support intervention. While within group analyses showed the Tai Chi group reported significant improvements in health-related QoL and the psychosocial support group declined at follow-up, between group analyses did not show a significant effect at 12-week follow-up. Clearly, this pilot RCT study was hindered by a very small sample size but it does, nevertheless, provide a basis for researchers to consider this question with greater rigour in future.

Two recent RCTs have explored the utility of yoga as a potential exercise option during rehabilitation from breast cancer treatment. Culos-Reed [63] compared the benefits of a 7-week yoga therapy programme with wait list control in cancer survivors, 85% of whom had been treated for breast cancer. There were significant group differences for psychosocial outcomes post-intervention but no significant differences in physical fitness. The authors suggested this may be due to the small sample size or perhaps the relatively short duration of the intervention. In a substantially larger RCT ($n = 128$) Moadel et al. [64] investigated the benefits of a 12-week programme of yoga in a multi-ethnic sample of breast cancer survivors, who were mostly of African American or Hispanic ethnicity. The yoga group ($n = 84$) reported significantly higher social well-being scores post-intervention than wait list controls ($n = 44$). No other differences reached statistical significance. The authors also highlighted the issue of adherence to the intervention, as a high proportion (31%) of study completers did not attend any group yoga classes, although some participants did complete yoga at home.

Taken together, the studies described here suggest that yoga and Tai Chi may be efficacious in promoting psychosocial health, but they may have less scope for enhancing physiological outcomes in this population. The trials described here are not without their methodological limitations and future research will need to address these before we have a clearer picture about the effects of ‘alternative’ types of exercise upon breast cancer survivors’ QoL.

4.4.2.6 Exercise Versus Other QoL Interventions

Cancer patients are traditionally offered a variety of ‘talking therapies’ (i.e. psychotherapy, meditation and relaxation) or access to support groups to assist them
in recovering from a diagnosis of cancer and subsequent treatments. Group psychotherapy is a popular ‘gold standard’ treatment in many cancer care contexts and has been shown to be effective in improving QoL in cancer survivors [65]. Given this, Courneya and colleagues [66] \((n = 108)\) evaluated the effectiveness of a home-based exercise intervention plus group psychotherapy versus group psychotherapy alone in cancer survivors. About 40% of the sample had been treated for breast cancer. The authors rationale for the trial was based on the premise that it was important to establish whether exercise is as effective in improving QoL beyond the best currently available intervention, rather than providing an alternative to them. Significant beneficial effects for QoL, particularly regarding functional QoL, fatigue and sum of skinfolds, were found for the exercise plus psychotherapy group at the end of the 10-week intervention. However, it is also important to note that no significant group differences in emotional and social well-being were found; although given that patients were receiving psychotherapy it was unlikely that the addition of exercise would substantially influence these outcomes. Nonetheless, this study suggests that exercise in combination with interventions, such as psychotherapy, can have a potent effect upon the QoL of cancer survivors. It remains to be seen whether exercise would prove to be as effective as standard QoL interventions when compared ‘head to head’ as single-component interventions. That said, if meta-analyses of the effects of exercise [67] and psychosocial interventions [16, 68] upon QoL are compared, exercise yields ESs that are at least comparable with psychosocial interventions, if not better.

### 4.5 Reviews and Meta-analyses

Several narrative reviews, systematic reviews and/or meta-analyses of the effects of exercise/PA interventions upon QoL and related health outcomes in breast cancer patients and survivors have been published. It is beyond the scope of this chapter to describe these in detail here and readers are directed to the publications for further information [35, 69–71].

One of the most recent systematic review and meta-analyses of RCTs that recruited women undergoing or recovering from breast cancer was published by McNeely et al. [67]. The authors identified 14 studies for inclusion of variable methodological quality, with only four considered to be of high quality. Significant heterogeneity was also found. The authors cautiously concluded that exercise is an effective intervention that improves QoL (WMD in FACT-G score: 4.6, CI: 0.35–8.80), peak oxygen consumption (SMD: 1.14, CI: 0.47–1.81), physical functioning (SMD: 0.84, CI: 0.36–1.32) and reducing symptoms of fatigue (SMD: 0.46, CI: 0.23–0.70), but called for larger trials of high methodological quality that include long-term follow-up. Several high(er) quality RCTs that post-date this systematic review and meta-analysis have been published and it might be that they will have addressed some, or all, of the methodological issues raised by the review authors.
4.6 ‘What’s It Like?’ Cancer Survivors’ Experiences of Exercise

While trials provide evidence of the effectiveness of an intervention, they do not provide any information on individuals’ experiences, attitudes and perceptions of an intervention. The following section describes a series of studies that have explored ‘what’s it like’ to participate in exercise interventions after treatment for cancer. We focus primarily on discussing studies that have included women with breast cancer, although studies involving other cancer types have also been published [72–75].

Using semi-structured interviews Stevinson and colleagues [76] explored the feasibility and acceptability of a 10-week group exercise rehabilitation programme for cancer patients, including those diagnosed with breast cancer. Most patients had completed curative treatment. During the interviews, participants indicated that they valued the group nature of the classes and that they provided a source of social support and generated a sense of solidarity and camaraderie. Some participants also appreciated the opportunity to meet and talk with other people who had had similar experiences. By engaging in the classes participants felt they were being proactive in their rehabilitation in a supportive environment. It was also interesting to note that some participants felt the classes were inconvenient because they involved relatively long and difficult journeys. Moreover, as found in other studies, travel problems were the biggest barrier to recruitment.

Race for Life is a charitable event organised by CRUK which involves women running or walking a set distance in parks and green spaces throughout the UK to raise money. Female cancer survivors who had participated in ‘Race for Life’ [77] were invited to be interviewed about their experiences. Participants reported that the race had helped make them feel less isolated as they shared the experience with many other female cancer survivors. Participants also commented that ‘Race for Life’ had aided their physical and psychological rehabilitation and helped them gain some sense of ‘normality’. Exercise was viewed as a vehicle for ‘moving forward’, which is an important outcome given that cancer survivors have often undergone lengthy and gruelling treatment regimens. Exercise might help to counteract some of the negative thoughts survivors have about their health by providing a step towards positive health action.

The psychosocial effects of dragon boat training and racing have been investigated through several qualitative studies [78–80]. Reports [78–80] have suggested that the physical and emotional common bond of ‘being in the same boat’ with fellow breast cancer survivors provides ‘an impetus for change’, and facilitates a shift from a negative life experience to one that is more positive and optimistic [78]. Furthermore, the competitive element and group dynamic of dragon boat racing have also been shown to provide participants with motivation to engage in a healthy, positive behaviour and give direction and focus to their training [80]. In other studies, participants have explained that dragon boat exercise offered an opportunity for regaining a sense of personal control [79], with the ability to alter self-perceptions, redefine individuals’ identity as athletes and facilitate positive psychological growth [80].
Similar to the findings from RCTs, these qualitative studies challenge commonly held beliefs amongst both cancer patients and cancer care health professionals that ‘rest is best’ after treatment for cancer. The studies outlined here also offer tremendous insight into the exercise experiences of cancer survivors and provide important information that may inform the development of exercise interventions in future studies. These studies remind us of the importance of the qualitative research paradigm in exploring individuals’ experiences of interventions and that findings from RCTs are only one kind of ‘evidence’ that can inform us about whether an intervention can impact upon particular outcomes.

4.7 What Next?

This field has grown enormously since the early studies in the 1980s [29–32] and continues to thrive. The first studies focused almost exclusively on assessing the benefits of supervised exercise programmes, perhaps because in the early days exercise was seen as ‘unsafe’ and should only be performed by cancer patients and survivors when under supervision. Trials of supervised programmes have been critical in demonstrating that exercise has the potential to not only improve QoL, but that it can be performed safely without undue adverse effects in these populations. As the evidence base has evolved, attention has moved towards considering the efficacy of home-based interventions as well as alternative activities such as yoga, Tai Chi and dragon boat racing. Despite these advancements, we must also recognise that many questions remain unanswered and further research needs to be conducted in a number of key areas.

With a few notable exceptions [57–59] many published studies to date have included small sample sizes and/or have not used formal power calculations to estimate the required sample size, resulting in numerous underpowered studies in this field. Whilst is it encouraging to see the literature base increasing, underpowered studies are not always helpful because they may fail to detect effects that are ‘real’ and subsequently dilute ESs in meta-analyses. Future studies must be appropriately powered and include adjustments to sample size calculations to account for the possibility of intervention contamination in no-exercise comparator groups. It is also important that the clinical relevance of findings is reported as this often allows results to be interpreted in a more meaningful way. Findings from one of our own trials [37] have demonstrated the need for attention control comparison groups when psychological outcomes are assessed.

While we have general guidelines on exercise prescription for cancer survivors [81, 82], so far there is little evidence to help identify the optimum mode, frequency, duration or intensity of activity required for beneficial QoL effects in breast cancer survivors and there has to be recognition that ‘one size may not fit all’[83]. Moreover, we already know [84] that demographic, medical, social cognitive and environment factors appear to influence the exercise preferences of breast cancer survivors. Future research that assesses the efficacy of individualised interventions,
taking into account these parameters, may be worthwhile. Additionally, the role that alternative modes of exercise might have in facilitating improvements in QoL needs to be considered. It is encouraging to see that studies of this type are emerging in the literature and we encourage further research in these areas.

Most studies have examined the effects of exercise adoption and there is a paucity of RCTs that have examined the issue of maintenance in breast cancer survivors. Hence, there is only limited understanding of the extent to which interventions are able to bring about sustained changes to PA levels and QoL. Moreover, it is very likely that cancer survivors will face substantial challenges in maintaining participation in regular exercise, as do the general population and individuals with other chronic illnesses. On a related issue, it is not known at present which type of exercise or PA is most likely to be adopted and maintained by breast cancer survivors. Whilst more costly and time consuming, it is imperative that trials are designed to include long-term follow-up so that maintenance issues can be explored.

At the time of writing, the overwhelming majority of survivors recruited into trials in this field have been white and from advantaged socio-economic backgrounds. Sub-groups of breast cancer survivors such as those who are socially more isolated and ethnic minority women may be at a greater risk for reduced QoL [85, 86]. These populations may well be more difficult to recruit but greater efforts need to be made to ensure that trials represent the wide spectrum of women that are affected by breast cancer. It is noteworthy that of the 128 participants recruited in the trial by Moadel et al. [64], 73 (45%) were either African American or Hispanic, demonstrating that these populations of women are willing to consider participation in trials involving exercise interventions when given appropriate opportunities to do so.

Little research has focussed on the translation and integration of exercise interventions into clinical practice. The use of oncologists to promote exercise during consultations was shown to be effective in one trial [59] but this approach may prove prohibitive due to the ever increasing number of cancer survivors who are seen in follow-up clinics and because of constraints on consultation times. Variations to this approach could be evaluated in future research, for example, it might be that other health professionals (i.e. cancer nurses and general practitioners, health trainers and physiotherapists) are able to provide prompts or lifestyle consultations to breast cancer patients in effective and cost-effective ways. The use of volunteers to promote exercise in cancer survivors has shown some promise of being efficacious and would appear to be a worthwhile avenue for further research.

The value of rehabilitation services is increasingly recognised as important to avoid health-care expenditure in the future and recent evidence involving healthy adults has reported that community-based PA programs offer good value for money [87]. Accurately establishing the financial cost of exercise rehabilitation services for cancer patients must now be an important direction for future research; this information is critical if we are to persuade health-care providers in the Western world of the value of exercise programmes for cancer survivors. Given the number of trials that have been published to date, it is rather surprising so little is known about the cost-effectiveness of exercise programmes during rehabilitation from cancer treatment.
4.8 Summary and Conclusions

The number of women who are treated successfully for breast cancer is high and length of survival also continues to grow. Therefore, long-term health issues specific to this population are fast emerging as an important public health concern. Evidence suggests that many of the physical, functional and emotional impairments that can be experienced by women during and after treatment for breast cancer may be ameliorated, at least in the short term, through participation in regular exercise, whether it is group or individual, aerobic or resistance, supervised and/or home based. Regardless of type, adherence to interventions has generally been good, further supporting the acceptability of exercise interventions to breast cancer survivors. There has been a preponderance of trials with short follow-up and the inclusion of long(er)-term follow-up should be a pre-requisite of any future trials; this will become even more critical as we move towards examining the benefits of exercise on survival outcomes. In the meantime, given that exercise is unlikely to cause harm, we must do everything possible to ensure that all breast cancer survivors are given the opportunity to be physically active, so that they can experience the therapeutic benefits that participation may be able to provide. Ultimately, this may optimise recovery from cancer treatment and improve the lives of the many women throughout the world, who are living as survivors of breast cancer.

Acknowledgments Amanda Daley is supported by a NIHR Senior Research Fellowship (Career Scientist Award). The views expressed in this publication are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health.

References


Chapter 5
The Importance of Controlling Body Weight After a Diagnosis of Breast Cancer: The Role of Diet and Exercise in Breast Cancer Patient Management

Michelle Harvie

Abstract Overweight and obesity occur in approximately 60% of patients at diagnosis of breast cancer and a further 60–75% gain weight during treatment, including those who were previously of a healthy weight. Excess adiposity is linked to increased mortality from breast cancer and from weight-related co-morbidities (e.g. CV disease and other cancers) and is a major psychological concern to patients. Data from recent randomised controlled trials suggest that weight control can reduce breast cancer recurrence by 24%. Weight control is not a routine part of breast cancer management for the majority of patients. Successful interventions are likely to require a combined diet and exercise approach and behaviour change counselling. Current evidence suggests that weight control has the potential to improve outcome and wellbeing for breast cancer patients, although the optimum timing, composition of the diet and delivery of interventions are important considerations for future research.

5.1 Trends in Breast Cancer Incidence and Mortality

Breast cancer is the most common malignancy amongst women in Western countries and typically accounts for 25–30% of all female cancers. Breast cancer also occurs in men but is a relatively rare occurrence (0.2% of cancers) [1]. Rates of breast cancer are increasing worldwide, particularly within Asian and developing countries, which traditionally had much lower rates [2]. Increased rates reflect global trends in lifestyle and hormonal reproductive risk factors, e.g. obesity, sedentary lifestyles and use of hormone replacement therapy. Interestingly, rates of oestrogen receptor-positive (ER-positive) breast cancer in the USA have recently declined by 13%, and this has been attributed to a decline in the use of hormone replacement therapy [3].

The majority of breast cancer cases (80%) occur in women aged 50 or over. Earlier detection and advances in adjuvant treatment have reduced mortality from
breast cancer, particularly amongst women aged 40–70 years. Between 1989 and 2006, breast cancer mortality in the UK fell by 43% in women aged 40–49, by 39% in women aged 50–64, by 37% in women aged 65–69, by 32% in women aged 15–39 and by 16% in women over 70 [4]. The most recent (and undoubtedly conservative) estimates indicate that there are approximately 2.5 million women living with a history of breast cancer in the USA and approx 550,000 in the UK [4, 5]. Thus, the long-term health and wellbeing of cancer patients is an increasingly important consideration for researchers and healthcare professionals alike.

5.2 Current Recommended Treatments

In countries with breast screening, approximately 60% of cancers are localised to the breast at the time of diagnosis (stages I and II), 30% have local lymph node involvement (stage III) and 10% are metastatic (stage IV) [5]. Patients with early breast cancer (stage I–III) usually have some form of breast surgery and this is followed by approximately 3 weeks of RT if they have had conservation surgery. Three quarters of breast cancers are oestrogen receptor positive (ER positive) in Western societies and ER-positive women receive adjuvant endocrine therapy. Standard treatment is a 5-year course of the selective oestrogen receptor modulator tamoxifen. Aromatase inhibitors (anastrozole, exemestane, letrozole) are also increasingly being used up front for women at high risk of recurrence and after 2–5 years of tamoxifen.

Approximately 25% of early stage patients receive adjuvant chemotherapy and 3% receive neoadjuvant chemotherapy. The 20% of patients with herceptin receptor (HER-2)-positive tumours receive targeted biological therapy, e.g. trastuzumab or lapatinib therapy. Women diagnosed with advanced metastatic disease receive either endocrine therapy or chemotherapy, whilst men with metastatic disease receive endocrine treatment. As the majority of male breast tumours are ER positive, most patients receive tamoxifen or aromatase inhibitors, whilst some individuals receive chemotherapy. The effects of these treatments on body weight and body composition have not been reported in men [6], and no studies have investigated the impact of weight-loss interventions on outcome in male breast cancer patients. Hence, the remainder of this chapter will be focused on female breast cancer.

5.3 The Problem of Excess Body Weight in Breast Cancer Patients

5.3.1 Prevalence of Overweight and Obesity Amongst Breast Cancer Patients

Most countries, including the USA and the UK, have experienced dramatic increases in the prevalence of overweight (BMI 25–29.9 kg.m⁻²) and obesity (BMI ≥ 30 kg m⁻²) over the past 20 years. In the UK the proportion of women estimated
to be either overweight or obese increased from 32% in 1984 to 59% in 2006 [7]. Comparable increases have also been seen amongst breast cancer patients. In 2003, an audit within our institution estimated that 36% of breast cancer patients are overweight (BMI 25–29.9 kg.m⁻²) and 25% are obese (BMI > 30 kg m⁻²) at the time of diagnosis (prior to treatment), compared to 20% who were overweight and 7% obese in 1980 [8]. As there was no difference in the age profile of women receiving treatment at these two time points, the increased body weight of our patients reflects higher body weights in the general population. Furthermore, approximately 63% of the 6,241 post-menopausal early breast cancer patients recruited to the international ATAC trial between 1996 and 2000 were overweight (39%) or obese (24%) [9]. This is likely to be a conservative estimate within the general clinic, as women recruited into clinical trials are known to be more health conscious.

5.3.2 Weight Gain After a Diagnosis of Breast Cancer

Many breast cancer patients experience weight gain, specifically gains in fat and loss of FFM (sarcopenic obesity) after diagnosis. Gains are greatest amongst women who are pre-menopausal, and receiving adjuvant chemotherapy, and amongst those who are thinner at diagnosis [10]. Historical data show that gains also occur in women not receiving adjuvant therapy, particularly women with a poorer prognosis, which may reflect the importance of changes in eating and exercise behaviour in response to the psychological distress of a breast cancer diagnosis [11]. We have previously reported prospective changes in body weight, body fat and energy balance amongst patients (n = 17) receiving adjuvant FEC and CMF chemotherapy. The principal findings were significant weight gain during chemotherapy and in the 6 months post-treatment. At 1-year, mean (±SE) weight gain in patients having had adjuvant chemotherapy was 5.0 (1.0) kg. There was also a significant increase in body fat of 7.1 (1.0) kg, particularly central fat, with a mean gain in waist circumference of 5.0 (1.0) cm. Gains in fat were partly accounted for by a decline in REE during chemotherapy and in the 3 months post-chemotherapy, low activity levels in the year after diagnosis and a failure to reduce energy intake [12] (Table 5.1). None of the patients had received steroids during treatment, hence disputing the widely held belief that gains in fat and loss of FFM in these patients are linked to the widespread short-term (1–2 days) use of steroids as an anti-emetic. Most current adjuvant chemotherapy regimens include anthracyclines, and more recent data show comparable gains with both anthracycline and non-anthracycline-based chemotherapy [13]. The majority of weight gain occurs during the first 2 years after diagnosis but it is not subsequently lost [13]. Interestingly, the weight gain that has been consistently observed in European and American cohorts [13, 14] was not reported in a recent cohort of 260 Korean patients [15].

There are few reported data on weight change during neoadjuvant chemotherapy. Data from our small sample (n = 6) showed a mean (±SE) weight loss of −2.3 (2.3)
kg during the neoadjuvant chemotherapy period but with rebound gains in the post-chemotherapy period. At 1 year, patients had gained 2.3 (2.6) kg in body weight and had experienced a significant gain in total fat of 4.7 (2.5) kg and a 4.7 (2.5) cm increase in waist circumference [16].

There is a perception amongst patients that tamoxifen and aromatase inhibitors lead to weight gain. Typically 40% of patients complain of ‘weight gain’ during adjuvant endocrine therapy [17], yet randomised studies have shown modest weight gains of 1–2 kg in both study and control patients [18]. We determined changes in body weight and body composition (body fat mass and FFM from skin folds, waist and hip circumference and abdominal skin fold) over the first year of treatment amongst 23 post-menopausal women receiving adjuvant anastrozole or tamoxifen. The mean (±SE) age of the group was 54.7 (0.8) years, BMI after surgery was 27.8 (1.2) kg m⁻², and percentage body fat was 39.0 (1.3)%. The modest weight gain in the endocrine group of 2.6 (0.8) kg was comparable to published figures for weight gain amongst healthy post-menopausal women of 2.1 (0.4) kg [19, 20]. Women receiving endocrine therapy appeared to have comparatively greater gains in total and particularly central fat (i.e. waist circumference and abdominal skin fold) and a greater loss of FFM compared to published data for healthy post-menopausal women [19, 20]. These changes were largely independent of weight change, highlighting the importance of assessing body composition in addition to body weight post-operatively. An increase in body fat and waist circumference explain the perceived weight gains of breast cancer patients that are referred to above.

Table 5.1 Change in body mass and composition in the year after diagnosis in women receiving adjuvant chemotherapy and adjuvant endocrine therapy (adapted from Harvie et al. [12] and Harvie and Howell [16])

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women receiving adjuvant chemotherapy, n = 17</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.3 (2.2)</td>
<td>+3.3 (1.0)*</td>
<td>+5.0 (1.0)**</td>
</tr>
<tr>
<td>Body fat (kg)</td>
<td>25.8 (1.5)</td>
<td>+4.0 (0.8)**</td>
<td>+7.1 (1.0)**</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>44.5 (2.0)</td>
<td>−0.5 (0.6)</td>
<td>−1.7 (0.6)*</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>84.8 (1.0)</td>
<td>+3.5 (1.0)*</td>
<td>+5.1 (1.0)**</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>103 (2.0)</td>
<td>+1.7 (0.9)</td>
<td>+3.6 (1.4)*</td>
</tr>
<tr>
<td>Abdominal skin fold (mm)</td>
<td>38 (3.4)</td>
<td>+9.7 (2.8)*</td>
<td>+16.2 (2.5)**</td>
</tr>
<tr>
<td><strong>Women receiving adjuvant endocrine therapy: tamoxifen or anastrozole, or combination, n = 23</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.7 (4.3)*</td>
<td>+1.0 (0.6)</td>
<td>+2.6 (0.8)*</td>
</tr>
<tr>
<td>Body fat (kg)</td>
<td>28.7 (2.6)</td>
<td>+1.8 (0.5)*</td>
<td>+4.2 (0.8)*</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>42.9 (1.7)</td>
<td>−0.8 (0.4)</td>
<td>−1.6 (0.5)*</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>89.3 (3.5)</td>
<td>+1.8 (0.9)*</td>
<td>+4.4 (1.3)**</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>103.6 (3.1)</td>
<td>+0.9 (0.8)</td>
<td>+2.4 (1.1)*</td>
</tr>
<tr>
<td>Abdominal skin fold (mm)</td>
<td>45.6 (2.4)</td>
<td>+6.3 (1.1)*</td>
<td>+11 (1.4)**</td>
</tr>
</tbody>
</table>

Mean (SE) *P<0.05; **P<0.01
Concerns about weight gain amongst such women may decrease compliance to these adjuvant agents.

Whether changes relate to breast cancer treatments or simply reflect the normal effects of inactivity and disinhibited eating amongst women recently diagnosed with breast cancer or recovering from breast surgery and RT is not known. Tamoxifen and aromatase inhibitors have differential effects on hormone systems, which in turn may exert different effects on fat mass and FFM, energy balance and weight gain. Tamoxifen has both oestrogen agonist and oestrogen antagonist actions and is known to lower circulating levels of IGF-1, increase leptin and limit hepatic fat oxidation [21]. Aromatase inhibitors reduce oestrogen levels, have a neutral effect on or increase IGF-I and reduce leptin levels [22]. There are few data on the differential effects of these agents on body composition but a recent randomised controlled trial of overweight or obese post-menopausal women who were switched to exemestane after 2 years of tamoxifen treatment showed reductions in fat mass at 1 year (–8%), whereas there was no change in women who remained on tamoxifen [23].

Advanced breast cancer patients do not develop the characteristic cachexia, hypermetabolism or anorexia reported for other cancers. We undertook an in-depth study of energy balance in patients with advanced breast cancer, to determine the reasons for this. We determined prospective measurements of body mass and body composition, REE, energy and protein intake over 4–6 months of chemotherapy in 10 patients with metastatic breast cancer. Patients increased their energy intake by a mean (95% CI) of 873 (266–1,480) kJ (P < 0.01), experienced declines in FFM and a 2.1 (0.8–3.5)% gain in body fat over the course of treatment. Gains in body fat were strongly correlated to mean energy intake throughout chemotherapy (Spearman’s correlation coefficient: 0.617; P<0.05). Thus, the ability to exceed energy requirements amongst patients with metastatic breast cancer leads to gains in body fat but does not prevent loss of FFM [24].

5.3.3 Impact of Obesity and Weight Gain on Breast Cancer Recurrence and Breast Cancer-Specific Mortality

Obese women are known to have a poorer breast cancer prognosis, which has been reported in more than 40 population studies. Some of this risk can be attributed to adverse prognostic factors at the time of diagnosis, e.g. a higher likelihood of ER-negative tumours and larger higher grade tumours with positive lymph nodes [25]. This is partly linked to delayed diagnosis but believed to be mainly caused by differences in the intrinsic biology of breast tumours, with more rapid development and progression due to the biochemical and hormonal environment in obese patients [26]. The adverse effects of obesity are, however, seen irrespective of tumour grade, stage and receptor status at diagnosis. A key question that remains unanswered is
whether the genetic characteristics of poor prognosis cancers in obese women can be modified by later weight loss to improve outcome [27].

5.3.4 The Effects of Weight Gain and Weight Loss After Diagnosis

A small body of literature has investigated the effects of weight gain or weight loss after diagnosis on outcome. Typically weight gain in excess of 5 kg has been linked to adverse prognosis, regardless of starting weight [28–30], though not in all studies [10]. There are few data on the effects of weight loss on outcome since this is a less likely occurrence. Importantly, the WINS, a large-scale randomised low-fat dietary intervention trial (see Section 5.6.2) found that weight control (approximately 3% relative difference between the two study arms) improved the 5 year disease-free survival HR for relapse events by 24% (HR: 0.76; 95% CI, 0.6–0.98; \( P = 0.08 \)) [31].

5.3.5 Effects of Obesity on Prognosis in Women Receiving Adjuvant Endocrine Therapy

The adverse effects of obesity in ER-positive tumours are thought to be associated with higher levels of bioavailable oestradiol, as a result of increased aromatization within adipocytes and lower circulating concentration levels of sex hormone-binding globulin [32]. Predictably, the adverse effects of body weight and weight gain on breast cancer prognosis have not been demonstrated in more recent studies of post-menopausal women, many of whom were receiving adjuvant anti-oestrogen therapy (i.e. tamoxifen or aromatase inhibitors) [29, 33–36]. Within the WINS study, weight loss was associated with greatest benefits amongst women with ER-negative tumours receiving chemotherapy (HR: 0.58; 95% CI, 0.37–0.91; \( P = 0.018 \)), but the effects were somewhat weaker and did not reach statistical significance in ER-positive women receiving tamoxifen (HR: 0.85; 95% CI, 0.63–1.14; \( P = 0.28 \)) [31].

The possibility that endocrine therapy may exert a greater protective effect amongst heavier women, on account of a greater relative reduction in oestradiol [37], and that the dose of aromatase inhibitor or tamoxifen may be inadequate amongst heavier women are both unlikely. Within the NSABP-14 trial, tamoxifen reduced the risk of recurrence by 40% compared with the placebo within normal, overweight and obese women [33]. Similarly, a recent analysis within the ATAC trial showed the efficacy of anastrozole was not modified by body weight [9]. Body weight does not appear to influence the metabolism of tamoxifen or the declines in oestradiol with aromatase inhibitors [38]. In summary, obesity does not appear to increase the risk of recurrence or breast cancer mortality amongst women receiving adjuvant endocrine therapy; however, evidence suggests that it does increase their risk of non-cancer deaths (see Section 5.5).
5.3.6 Effects of Obesity on Prognosis in Women Receiving Adjuvant Chemotherapy

Some of the adverse effects of obesity on prognosis in chemotherapy cohorts may be due to the historic practice of under dosing chemotherapy for heavier women [39]. However, recent evidence from two large studies, which included approximately 2,500 patients with stage I, II, or III breast cancer [40] and 600 with locally advanced stage III breast cancer [41] who received doses based on actual body weight (and also accounted for other prognostic factors) suggested that overweight and obesity are independent adverse prognostic factors, decreasing disease-free and overall survival by 10–12%. Furthermore, recent prospective data on 1,200 patients receiving neoadjuvant chemotherapy from the MD Anderson Centre in the USA showed that overweight and obese patients were less likely to have a pathological complete response (defined as no residual invasive carcinoma in either the breast or the axillary lymph nodes) compared to their normal or underweight counterparts (OR: 0.67; 95% CI, 0.45–0.99) and had worse overall all-cause mortality over 10 years (OR: 1.65; 95% CI, 1.18–2.3). The mechanism of poorer prognosis amongst overweight women with ER-negative tumours receiving chemotherapy has not been elucidated but is thought to be mediated by the adverse hormonal and secretory effects of adipose tissue, including higher circulating levels of insulin, leptin, inflammatory markers and lower adiponectin levels [42], in addition to increased cell proliferation [43]. Some reports suggest a greater clearance of certain chemotherapy agents in heavier women [44], though not others [45].

5.3.7 Effects of Obesity on Prognosis in Women with Metastatic Breast Cancer

Few studies have investigated the effects of body weight on outcome in metastatic breast cancer patients. A study amongst 200 patients with advanced breast cancer found that body weight did not influence the response to tamoxifen [46]. Paradoxically a recent small-scale study amongst 42 patients receiving anastrozole reported that those with greater central obesity had longer overall survival and progression-free survival than their leaner counterparts. The authors suggested that this may have reflected lower levels of IGF-1 alongside central obesity [47].

5.3.8 Obesity and Contra-Lateral Breast Cancer

Women diagnosed with breast cancer are at higher risk of developing breast cancer in the opposite (contra-lateral) breast. For post-menopausal women, the risk is estimated to be approximately 0.6% each year and is significantly reduced by tamoxifen (50%). Data from the NSAPB-14 study showed that obese women are at
increased risk of developing contra-lateral breast cancer despite the use of tamoxifen, compared to their normal weight counterparts. Within this study, the 10-year cumulative incidence of contra-lateral breast cancer in obese women was 5.6%, compared with 3.3% in underweight to normal weight women (HR: 1.58; 95% CI, 1.1–2.5, P<0.05) [33].

5.3.9 The Effect of Central Obesity and Insulin Resistance on Prognosis

An increasing body of evidence links central obesity, higher levels of circulating insulin and increased insulin resistance to higher rates of breast cancer relapse. Borugian and colleagues reported the RR of breast cancer mortality for each 0.1 unit increase in waist:hip ratio to be 1.4 (95% CI, 0.9–2.1) [48]. Comparable findings were seen in a cohort of young breast cancer patients [49]. Four large prospective studies of patients recruited during the 1980s and early 1990s also reported a threefold increase in recurrence or death in women with the highest quartile of circulating insulin, though this has not been a consistent finding [49]. A recent commentary by Goodwin suggested that a 25% reduction in circulating insulin (seen typically with 5% weight loss) could lead to 5–6% absolute improvements in outcome, comparable to those seen with adjuvant chemotherapy [50]. Interpretation of the effects of insulin from these historic cohorts may, however, be confounded by the significant proportions of ER-positive women who were not receiving adjuvant anti-oestrogen therapy, since insulin may be serving as a proxy for increased circulating oestradiol. Three ongoing studies are assessing the effects of central obesity and insulin sensitivity on outcome alongside current treatments. First the POSH study is examining the effects of central obesity and weight gain on outcome in approximately 750 breast cancer patients aged younger than 40 or 40–50 with a BRCA mutation [51]. Furthermore a recent review describes two large-scale randomised controlled trials which are examining the effects of metformin and a combined diet and exercise weight control intervention on insulin sensitivity and outcome in early breast cancer patients [52]. Excess adiposity is not likely to impact upon prognosis via its effects on the IGF-1 axis as both general and central obesity have been consistently linked to lower circulating levels of IGF [53, 54].

5.4 Body Weight and Lymphoedema

Lymphoedema is an undesirable complication following axillary clearance or RT to the axilla, which can have negative physical and psychological effects on women. Obesity is a risk factor for the development of lymphoedema [55], possibly due to an increased risk of post-operative infections, coupled with the increased likelihood of technical problems during axillary surgery amongst heavier women.
A small randomised trial examined the effects of a weight reduction diet compared to no dietary intervention in overweight women with lymphoedema. Women wore compression hosiery as part of their usual lymphoedema management, and 11 women were randomised to a 1,000 kcal energy deficit diet or to a control group over 12 weeks. Excess arm volume, as measured by circumference measurements, was reduced from the mean (±SD) excess of 25(7)% to 15(10)% in the intervention group and was unchanged in the control group ($P < 0.05$). The mechanism whereby weight reduction helps to reduce arm volume is not known and warrants further investigation. Possible factors include anti-inflammatory effects, reduced effectiveness of compression hosiery or local effects on lymphatic flow [56].

5.5 Obesity-Related Co-morbidities in Breast Cancer Patients

Many post-menopausal breast cancer patients have obesity-related co-morbidities at the time of diagnosis, such as hypertension (25–50%), coronary heart disease (15–27%), vascular disease (3–5%) and NIDDM (5–10%) [57]. Likewise, pre-menopausal patients also experience hypertension (18%) and hyperlipidaemia (cholesterol > 6.9 mol.L$^{-1}$; 25%) [58].

Stage of breast cancer is the strongest prognostic indicator of survival for breast cancer patients of any age. Co-morbidities are, however, a major cause of mortality amongst women diagnosed with localised breast cancer and this is particularly true for older women [59]. A recent SEER program report based on 220,263 patients with localised disease found that the cumulative probability of death from breast cancer over 28 years of follow-up from diagnosis was 0.21–0.28 in women younger than 50 years and 0.14–0.28 in women aged over 50 [59]. The major competing causes of death were CV disease and other cancers (Table 5.2).

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>CV disease (%)</th>
<th>Other cancers (%)</th>
<th>Respiratory disease (%)</th>
<th>Other disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White patients</td>
<td>4,427</td>
<td>15.7</td>
<td>35.2</td>
<td>5.6</td>
<td>43.5</td>
</tr>
<tr>
<td>Black patients</td>
<td>809</td>
<td>21.3</td>
<td>26.7</td>
<td>5.6</td>
<td>46.5</td>
</tr>
<tr>
<td>50–59 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White patients</td>
<td>8,332</td>
<td>27.8</td>
<td>32.4</td>
<td>8.3</td>
<td>31.5</td>
</tr>
<tr>
<td>Black patients</td>
<td>1,006</td>
<td>36.8</td>
<td>26.0</td>
<td>4.9</td>
<td>32.3</td>
</tr>
<tr>
<td>60–69 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White patients</td>
<td>18,661</td>
<td>37.0</td>
<td>26.0</td>
<td>9.6</td>
<td>26.4</td>
</tr>
<tr>
<td>Black patients</td>
<td>1,676</td>
<td>43.0</td>
<td>21.4</td>
<td>7.1</td>
<td>28.6</td>
</tr>
<tr>
<td>≥70 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White patients</td>
<td>49,837</td>
<td>53.0</td>
<td>13.8</td>
<td>9.9</td>
<td>23.3</td>
</tr>
<tr>
<td>Black patients</td>
<td>2,915</td>
<td>51.4</td>
<td>15.6</td>
<td>5.8</td>
<td>27.2</td>
</tr>
</tbody>
</table>
Excess body weight at diagnosis and weight gain during treatment may exacerbate existing co-morbidities or increase the likelihood of additional ones developing. As previously discussed, obese women receiving endocrine therapy are not necessarily more likely to die from breast cancer but they are at increased risk of dying from co-morbidities (HR: 1.49; 95% CI, 1.15–1.92) and of developing other cancers such as endometrial cancer [33]. Furthermore, cohort studies have shown that the presence of co-morbidities decreases overall survival but not breast cancer-specific survival. The decreased risk of all-cause mortality is illustrated by HRs (95% CI) of 1.85 (1.47–2.32) for diabetes, 1.65 (1.37–1.99) for hypertension and 1.78 (1.35–2.35) for CV disease [60, 61]. Another cohort study of 540 patients taking tamoxifen, however, found increased breast cancer mortality in patients with diabetes ($n = 82$) compared with those without diabetes ($n = 458$) (HR: 2.4, $P<0.006$), whereas diabetes did not affect prognosis in women receiving adjuvant chemotherapy [62]. In the latter study, the relatively small numbers of patients receiving adjuvant therapy ($82$ tamoxifen and $62$ chemotherapy) limit the validity of these findings. Nevertheless, the consistent adverse effects of co-morbidities on overall survival emphasises the importance of managing co-morbid conditions alongside breast cancer treatments [60, 61].

5.6 Interventions for Weight Control Amongst Breast Cancer Patients

5.6.1 Diet and Exercise Interventions

As highlighted earlier, in excess of 40 population studies have reported the adverse effects of body weight or weight gain on breast cancer prognosis. Despite this, however, there have been surprisingly few studies of weight reduction in breast cancer patients. The first demonstration that weight loss was feasible amongst breast cancer survivors was a randomised, calorie-restricted weight-loss intervention amongst post-menopausal breast cancer patients reported in 1993 [63]. Plans for a larger follow-up study were abandoned on the assumption that any potential benefits of weight loss on survival would be negated by the widespread introduction of adjuvant tamoxifen therapy.

Evidence suggests that weight control, specifically loss of fat and maintenance of FFM, requires a combined diet and exercise approach. A systematic review of approximately 900 weight-loss participants reported superior reductions in fat and minimal loss of FFM over 6 months with diet and aerobic exercise (−9 kg fat, −2 kg FFM) and diet only (−7.5 kg fat, −2.5 kg FFM), compared to aerobic exercise only (−2.9 kg fat, no change in FFM) and strength training (−1.5 kg fat, 1.3 kg increase in FFM) [64].

Goodwin et al. showed that weight gain was prevented in 61 women receiving adjuvant chemotherapy participating in a multidisciplinary 20-week diet and exercise programme. Five women developed recurrence and one died of a sub-arachnoid
haemorrhage, whilst the 55 women who completed the trial lost a mean (±SD) body weight of 0.53 (3.72) kg [65]. Not surprisingly, previous diet-only or exercise-only interventions during breast cancer treatment have been unsuccessful at limiting weight gain. For example, monthly dietetic counselling over 6 months of chemotherapy led to small non-significant reductions in weight gain during adjuvant chemotherapy: Gains of 2.0 kg were observed in the dietitian counselling group versus 3.5 kg in the control group (P = 0.4) [66]. Likewise a recent overview of women receiving adjuvant therapy showed a mean (95% CI) weight loss for an exercise-only group (compared to controls) of −1.1 kg (−2.44 to 0.22) [67]. Some randomised trials reviewed by Ingram et al. do show beneficial reductions in body fat with exercise interventions in breast cancer patients during chemotherapy (n = 1), RT (n = 1) and after treatments (n = 2), whilst other trials have failed to demonstrate these benefits (n = 3) [68].

Demark-Wahnefried et al. recently published a randomised feasibility study of diet, exercise and weight control during adjuvant chemotherapy. In the Survivor Training for Enhancing Total Health (STRENGTH) trial [69], pre-menopausal patients were randomised to either a high-calcium diet control group (n = 29), a calcium rich diet plus home-based exercise program (30 min >3 times.week−1; [n = 29]), or a calcium-rich, low-fat, high fruit and vegetable diet plus exercise program (n = 32) during the first 6 months of adjuvant treatment. Measures of adiposity were generally lower in the diet plus exercise groups but the only significant change was in percentage fat in the arms and legs (P = 0.047). The limited success of this intervention reflects the modest reduction in energy intake with the low-fat dietary intervention and this factor might also, in part, account for the modest weight loss seen when a home-based mail and phone intervention was tested in older breast cancer patients, as compared to an attention control group (change in BMI over 6 months was −0.1 kg.m−2 vs. +0.4 kg m−2) [70]. An individually prescribed energy deficit would inevitably have given a greater result [71].

5.6.2 Diet and Exercise Recommendations for Breast Cancer Patients

The optimum level of fat intake for weight loss in breast cancer patients requires careful consideration. In the recent WINS study, women consuming approximately 30 g fat per day (20% energy as fat) had a 24% reduction in relapse compared to women consuming on average 50 g.day−1 (30% energy as fat). The authors acknowledged that it is impossible to disentangle the effects of the fat reduction from the concomitant reduction in body weight, which also occurred (approximately 3% relative difference between the two study arms) [31]. The lack of effect on outcome of a comparable low-fat intervention in the WHELS, in which women did not lose weight [72], suggests that energy restriction and weight loss are likely to be more important than dietary fat restriction. Diets should, however, be limited in saturated fat, which may have a positive association with breast cancer and is well
known to increase risk of heart disease [73]. Replacing saturated with monounsaturated or omega-3 fats may prove to be beneficial for breast cancer patients. Moderate fat diets including 30–35% energy from fat but only 7% saturated fat are known to be superior to very low-fat eating plans (20% energy as fat) for limiting calorie intake and for weight loss on account of their higher satiety [74]. These diets are also superior for reducing insulin resistance [75] and the risk of CV disease [76].

There is much interest in the potential anti-cancer effects of fruit and vegetables, specifically the potential effects of carotenoids on cellular differentiation and apoptosis [77] and brassicas on oestrogen metabolism [78]. A recent large-scale randomised controlled trial of a high fruit and vegetable (13 servings.day$^{-1}$) and low-fat diet plan (20% energy fat) amongst 3,088 early-stage breast cancer patients, however, did not find beneficial effects in terms of breast cancer recurrence or mortality, despite good compliance to the interventions [72]. The intervention group consumed 10–13 portions.day$^{-1}$ compared to 5–7 in the control group. Over the mean 7.3 years of follow-up, 256 women in the intervention group (16.7%) compared to 262 in the comparison group (16.9%) experienced an invasive breast cancer event (adjusted HR: 0.96; 95% CI, 0.80–1.14; $P = 0.63$), and 155 intervention group women (10.1%) compared to 160 comparison group women (10.3%) died (adjusted HR: 0.91; 95% CI, 0.72–1.15; $P = 0.43$). Fruit and vegetables are an important part of a healthy weight control diet and can increase satiety [79] but need to be included as part of an overall calorie-controlled diet.

A number of other dietary factors may also influence the outcome for breast cancer patients. Alcohol is a well-established risk factor for the development of breast cancer [80]. However, a recent overview reported that none of the eight studies examining the effect of alcohol on breast cancer prognosis linked alcohol with survival [81]. Alcohol restriction is, however, prudent for weight control due to its intrinsic calorie content and appetite-stimulating effects. Fibre is an important component for weight loss and has additional beneficial effects on insulin sensitivity [82].

Exercise alone does not appear to control body weight amongst post-menopausal breast cancer survivors [67]; however, it is clearly a vital component of energy balance in weight control programs. Exercise has been associated with independent benefits on disease-free survival [83], QoL and CV fitness [67] and bone density [84]. Optimum weight control requires 45–60 min of PA per day [85].

### 5.6.3 Delivery of Weight-Management Programs for Breast Cancer Patients

The level of support required to achieve and maintain weight loss varies widely between individuals. In the non-cancer setting, sufficiently motivated individuals (approximately 9%) can lose weight on their own after discussing the options with their healthcare practitioner [86]. Weight control in non-cancer patients is more
effective when a combined diet and exercise approach is used, with a proportion of individuals also requiring behavioural counselling or adjunctive pharmacological therapies. Such combined approaches have not been tested amongst breast cancer patients. Weight management can be delivered via a one to one or group setting. People will have preferences for group or individual approaches and matching treatment to preferences provides better results [87]. Obese breast cancer survivors receiving group-based interventions appear to require additional individual behavioural counselling and support, which most likely reflects psychological issues in heavier patients. In a study by Djuric and colleagues, mean (±SD) weight loss over 12 months in a commercial slimming group was 2.7 (2.1) kg compared with 8.0 (1.9) kg in an individually counselled group and 9.5 (2.7) kg in a group attending the slimming group with additional individual counselling [88]. The timing of interventions needs careful consideration, as attempts to deliver lifestyle advice too soon after diagnosis may worsen the feeling of guilt and the psychological impact of a breast cancer diagnosis. In addition, disruptions to daily activities at this time could present barriers to changing diet and exercise behaviour. Equally the diagnosis of breast cancer is known to be a time when women may be more responsive to lifestyle change. Our own research and a study in the USA have indicated that approximately 70% of patients would wish to receive lifestyle advice in the 6 months immediately after diagnosis [89, 90].

5.6.4 Pharmacotherapy

Some patients may require additional pharmacotherapy for weight loss. The agents orlistat (Xenical®, Roche) and sibutramine (Meridia®/Reductil®, Abbott) are currently available for weight management in the general population. Neither agent has been linked to the development of breast cancer. Orlistat is a specific inhibitor of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat, allowing 30% of dietary fat to pass through the gut unabsorbed. Orlistat has been associated with a mean additional weight loss of 3.2 kg (95% CI, 4.15–2.37) compared with standard dietary advice [91]. Patients are advised to follow a hypo-caloric diet containing less than 30% of energy from fat since high-fat diets lead to steatorrhoea, flatus and faecal urgency. Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E and K), therefore diets rich in fruit and vegetables should be encouraged, whilst vitamin D status should also be considered amongst women at risk of osteoporosis or osteopaenia. Sibutramine inhibits the uptake of serotonin and norepinephrine in the brain and has been linked with a mean additional weight loss of 3.4 kg (95% CI, 4.45–2.35) compared with standard dietary advice [91]. Weight loss is achieved through early satiety, with a reported 20% reduction in food intake, whilst sympathetically mediated thermogenesis maintains the basal metabolic rate, which normally decreases as weight is lost. Sibutramine is contraindicated in patients with a history of psychiatric illness, depression or eating disorders and in those with hypertension.
5.6.5 Monitoring Patients in Weight-Loss Interventions

Body weight is a poor measure of changes in body fat mass and FFM in cancer patients. Body fat is best assessed using imaging techniques such as DXA, for total body fat, and MRI or CT for visceral fat stores. These techniques are expensive and not routinely available for the majority of patients, hence simpler methods such as bioelectrical impedance are increasingly used. Impedance is the resistance of the body to an alternating current. This technique is based on the fact that lean tissues have a high water and electrolyte content and are good conductors, whereas fat is a poor conductor. Impedance measurement is thus related to the volume of the conductor, which relates to the amount of body water FFM and fat mass. Impedance has been shown to reflect changes in body fat with weight loss in non-cancer patients [92]. We are currently validating bioelectrical impedance against a criterion method of DXA to assess its ability to accurately measure changes in FFM amongst patients receiving adjuvant chemotherapy and endocrine therapy. Increases in extracellular water amongst patients undergoing chemotherapy, however, may lead to fat stores being underestimated.

Waist circumference should be monitored as a proxy measurement of central fat stores (particularly visceral fat) [93]. Waist circumference is a potential marker for breast cancer prognosis, insulin sensitivity, CV disease and type 2 diabetes [48, 94]. A waist circumference that is greater than 35 inches (88 cm) amongst non-Asian women and greater than 32 inches (80 cm) for women of South Asian descent places them at a substantially increased risk of insulin resistance and the metabolic syndrome [95].

5.7 Weight Loss and Bone Health

Bone health is an important consideration amongst breast cancer patients, particularly those with a chemotherapy-induced menopause and those prescribed aromatase inhibitors [96], as bone density may be compromised further with weight loss. In healthy subjects a 4–13% weight loss leads to a 1–4% decrease in bone mass. Reductions in bone mass are greater with rapid weight loss and in older patients. These losses can be attenuated by ensuring that there is adequate intake of calcium (1,200–500 mg.day⁻¹) and vitamin D (10 μg.day⁻¹) from the diet and/or supplements. Weight-bearing exercise provides some benefits, and bisphosphonates are known to offset the reductions in bone density with weight loss [97].

5.8 Weight Loss and Quality of Life

The diagnosis and treatment of breast cancer can exert a significant psychological impact for women of all ages [98]. The most common long-term psychological effects include body image problems, mood disorders, anxiety, fatigue and problems
with sexual functioning [99]. Weight gain is cited as a major concern amongst early breast cancer patients [100, 101]. Weight gain has a negative impact on QoL in non-cancer patients, whilst modest improvements have been seen with weight loss [102]. Improvements in QoL have been reported in participants on a diet and exercise program to prevent weight gain during adjuvant treatment, which may reflect the well-known beneficial effects of exercise and weight management on this outcome [65].

5.9 What Advice Do Patients Want About Diet and Weight Control?

Breast cancer patients often seek information about their disease, particularly concerning the potential benefits of a healthy diet. However, in many countries, women have limited access to dietetic and physiotherapy services. For example, a survey amongst 355 breast cancer patients from Australia and Finland highlighted the fact that only 24% had received dietary advice from healthcare professionals and a third of patients had unmet needs for dietary advice [103].

We recently conducted a needs assessment survey for diet, exercise and weight control information amongst 100 consecutive early breast cancer patients (in situ to stage 3A) attending surgical review in our institution [90]. We surveyed women diagnosed between 6 months and 3 years previously and included patients who had received adjuvant chemotherapy and/or endocrine or RT (n = 45) and adjuvant endocrine therapy and/or RT only (n = 55) to ascertain any specific needs for advice in these two groups.

A total of 100 out of 110 patients who were approached completed the self-administered survey (91% response rate). Demographics and responses of the two groups of patients are shown in Table 5.3. Only 32% of all patients had received lifestyle advice from the hospital and 10% from their GP. A further 34% had sought advice from books, magazines or the internet and 5% from friends and other patients. Chemotherapy patients were more likely to seek information from the media (p = 0.05). Dietary change since diagnosis was more commonly reported amongst women receiving chemotherapy (p = 0.04). Although 71% of these patients reported weight gain since diagnosis, the most common cited dietary changes did not target weight control and included popular (non-evidence based) lay belief, such as increasing fruit and vegetable consumption and having less or no dairy products or red meat. Many of the patients did not engage in regular exercise and women in both groups reported increased and decreased activity levels since diagnosis. The majority of patients, particularly those who had received chemotherapy, had unmet needs for lifestyle advice. Chemotherapy patients were more likely to want exercise advice (p = 0.02). Many in both groups would have preferred to receive advice within a few weeks of diagnosis or after they had finished initial treatment and stated a preference for written advice or one-to-one consultations rather than hospital-based group education sessions.
Table 5.3 Characteristics and responses of early-stage breast cancer patients who received chemotherapy or RT and or endocrine therapy only in a patient and healthcare professional survey [90]

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy and/or endocrine or RT (N = 45)</th>
<th>Endocrine therapy and/or RT only (N = 55)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age (years)*</td>
<td>45(27–65)</td>
<td>54(39–69)</td>
<td>0.00</td>
</tr>
<tr>
<td>Time from diagnosis (months)*</td>
<td>20.2(6–34)</td>
<td>19.3(6–41)</td>
<td>0.89</td>
</tr>
<tr>
<td>Treatment received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT (%)</td>
<td>87</td>
<td>73</td>
<td>0.09</td>
</tr>
<tr>
<td>Endocrine (%)</td>
<td>76</td>
<td>80</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>BMI (kg.m⁻²)</strong></td>
<td>26.5 (17.8–50.5)</td>
<td>26.5 (15.4–46)</td>
<td>0.75</td>
</tr>
<tr>
<td>Overweight (%)</td>
<td>36</td>
<td>34</td>
<td>0.89</td>
</tr>
<tr>
<td>Obese (%)</td>
<td>29</td>
<td>26</td>
<td>0.89</td>
</tr>
<tr>
<td>Weight gain since diagnosis (%)</td>
<td>71</td>
<td>41</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Lifestyle change since diagnosis (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any change in diet</td>
<td>62</td>
<td>42</td>
<td>0.04</td>
</tr>
<tr>
<td>Increased fruit and vegetables</td>
<td>30</td>
<td>18</td>
<td>0.21</td>
</tr>
<tr>
<td>Limit/avoid dairy</td>
<td>13</td>
<td>5</td>
<td>0.08</td>
</tr>
<tr>
<td>Limit/avoid red meat</td>
<td>18</td>
<td>6</td>
<td>0.05</td>
</tr>
<tr>
<td>Increase in activity level</td>
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<td>17</td>
<td>0.08</td>
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<tr>
<td>Decrease in activity level</td>
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<td>0.08</td>
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<tr>
<td>No current regular exercise</td>
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<td>31</td>
<td>0.60</td>
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<tr>
<td>Sources of lifestyle advice (%)</td>
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<td></td>
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<tr>
<td>Hospital</td>
<td>33</td>
<td>31</td>
<td>0.83</td>
</tr>
<tr>
<td>GP</td>
<td>7</td>
<td>12</td>
<td>0.35</td>
</tr>
<tr>
<td>Books/internet</td>
<td>33</td>
<td>35</td>
<td>0.90</td>
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<tr>
<td>Media</td>
<td>21</td>
<td>8</td>
<td>0.05</td>
</tr>
<tr>
<td>Cancer helpline</td>
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<td>7</td>
<td>0.10</td>
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<tr>
<td>Friends/other patients</td>
<td>19</td>
<td>12</td>
<td>0.53</td>
</tr>
<tr>
<td>Unmet need for advice (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Bone health</td>
<td>47</td>
<td>38</td>
<td>0.44</td>
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<td>42</td>
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<td>0.36</td>
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<tr>
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<td>33</td>
<td>0.36</td>
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<tr>
<td>Exercise</td>
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<td>0.02</td>
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<td>Heart health</td>
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<tr>
<td>Smoking cessation</td>
<td>11</td>
<td>11</td>
<td>0.97</td>
</tr>
<tr>
<td>Preferred format of advice (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within a few weeks of diagnosis</td>
<td>45</td>
<td>37</td>
<td>0.44</td>
</tr>
<tr>
<td>After completing initial radio/chemotherapy</td>
<td>27 33</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Written advice only</td>
<td>36</td>
<td>34</td>
<td>0.36</td>
</tr>
<tr>
<td>One-to-one consultations</td>
<td>34</td>
<td>25</td>
<td>0.36</td>
</tr>
<tr>
<td>Group education sessions</td>
<td>13</td>
<td>10</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*median (range)
The high uptake to this survey increases the validity of our findings. Many patients had an unmet need for dietary advice and had made non-evidence-based lifestyle changes. This was especially the case amongst women receiving chemotherapy, which may reflect their younger age or greater concerns of recurrence. Many patients would welcome advice from their breast cancer team in the early stages after diagnosis. Although patient preference was for simple written advice only, successful diet and exercise behaviour change interventions would require ongoing advice, monitoring and support [104].

5.10 HealthCare Professional Survey: Current Roles and Attitudes to Delivering Diet, Exercise and Weight Control Advice to Early Breast Cancer Patients

BCNs, medical and clinical oncologists, breast surgeons and dietitians are potential deliverers of diet, exercise and weight control advice to breast cancer patients. We sought to evaluate their current roles and attitudes to the delivery of this advice using a mailed survey in July 2005. Thirty-two out of 147 BCNs (22%) who had attended a national BCN conference, 9/11 (82%) of consultant medical and clinical oncologists, 10/12 (83%) of consultant breast surgeons and 39/49 (79%) of dietitians randomly selected from the North West of England and from the National British Dietetics Association Specialist Oncology Group responded to a mailed survey. Only 9/39 (23%) of the dietitians had ever advised breast cancer patients and this was on a sporadic basis. Given their lack of experience of dealing with breast cancer patients, we did not include the dietitian views in our analysis.

5.10.1 Current Practice

In the UK, 47% of the BCNs and 37% of the consultants had discussed weight loss with breast cancer patients. Advice was not routine, however, but was provided to patients who specifically asked for it or who were obese or undergoing breast reconstruction. Advice to prevent weight gain after diagnosis was given by 61% of the BCNs and 53% of the consultants. Exercise was specifically encouraged by 34% of the BCNs and 26% of the consultants, again on an ad hoc basis.

5.10.2 Beliefs

The majority of BCNs and consultants felt that weight control should be a part of breast cancer patient management (BCNs 78% and consultants 84%). The remaining BCNs (22%) thought that weight was a sensitive subject, which they did not wish to raise with patients, whilst 16% of consultants cited organizational issues, inadequate staffing levels and regarded it as a low priority. BCNs most commonly cited
the reduction of co-morbidities (28%) and psychological benefits (17%) as a reason for interventions, whilst consultants cited reductions of breast cancer recurrence (38%) and improved body image (32%).

BCNs were more likely than consultants to think that specific exercise advice should be provided (91% compared with 63% of consultants). Nurses’ motivations for exercise interventions were to reduce fatigue (31%), to improve psychological wellbeing (28%) and for weight control (14%). Consultants thought that exercise should be used to aid weight control (42%), for psychological benefits (33%) and to reduce the risk of recurrence (17%). Again, organisational issues were identified as a barrier to offering exercise interventions by consultants.

The poor response rate amongst BCNs and the small numbers of breast surgeons and oncologists surveyed limits the ability to generalise our findings. However, our survey highlights some important beliefs and barriers to delivering interventions amongst breast cancer healthcare professionals, including concerns of burdening patients with additional worry or guilt, and practical issues of lack of time, inadequate skills and training.

Other surveys in Canada and the UK report that exercise is recommended by approximately 40% of medical staff, more so amongst oncologists than breast surgeons [105]. Likewise, De Guidice et al. found that oncology nurses were more likely to recommend weight management than oncologists (47% vs. 24%). The perception amongst medical staff that lifestyle interventions should be delivered by oncology nurses or physiotherapists and their reticence to be involved is a potential barrier to uptake [106]. Our survey highlights the fact that nurse-led interventions would only become feasible with additional training. Additional physician involvement would undoubtedly lend credence, and most likely adherence, to weight loss advice [107].

5.11 Summary and Conclusions

Weight problems are prevalent amongst early breast cancer patients, whilst gains in fat and loss of FFM typically occur during adjuvant treatment. Excess adiposity is linked to a poorer outcome, in terms of breast cancer recurrence, death from other weight-related conditions (i.e. CV disease and other cancers) and risk of lymphoedema. Data from recent randomised controlled trials suggest that weight loss can reduce the chances of recurrence and moderate existing lymphoedema. Weight issues are also a major concern amongst breast cancer patients but they are not addressed in routine clinical practice.

Future research priorities in this field should test pragmatic, cost-effective weight control interventions, explore patient-centred behaviour change, determine the prevalence of weight problems and their impact on outcome within current treatment trial cohorts, develop prognostic markers to act as surrogate endpoints for diet and exercise trials, and explore the role of weight control and energy restriction in advanced cancer.
References


Chapter 6
The Biological Mechanisms by Which Physical Activity Might Have an Impact on Outcome/Prognosis After a Breast Cancer Diagnosis

Melinda L. Irwin

Abstract Despite the growing body of observational evidence suggesting a link between PA and breast cancer survival, the mechanisms underlying this relationship are poorly understood. A few small RCTs have examined the impact of exercise on surrogate/biological markers of survival. The beneficial effects of PA may be mediated through a reduction in body fat and beneficial changes in metabolic (e.g., insulin) and sex hormones (e.g., androgens and estrogens), growth factors (IGF-I and associated binding proteins, e.g., IGFBP-3), adipokines (e.g., leptin, adiponectin), and/or inflammation (e.g., CRP). Although much further research is needed to determine the effect of PA on these biological markers, we posit that PA decreases breast cancer death directly and indirectly through multiple, interrelated actions of body fat levels and/or hormonal concentrations and actions. Given the high level of physical inactivity in the population, and the heavy burden that breast cancer creates for the individual and for society, the need for well-designed trials of exercise on breast cancer survival and surrogate/biological markers mediating a potential effect is an urgent public health priority.

6.1 Introduction

Breast cancer is the most frequently diagnosed invasive cancer among women [1]. Given the number of women affected by this disease, there has been significant research directed toward lowering breast cancer rates and improving outcomes in affected women. Although there has been extensive research looking at PA in the prevention of breast cancer [2], there is more limited evidence regarding the impact of exercise on breast cancer prognosis, specifically disease-free survival and
surrogate/biological markers of survival. However, numerous papers have recently been published focusing on associations between PA and breast cancer survival, as well as the effect of exercise on surrogate/biological markers potentially mediating the observed association between PA and breast cancer survival. The primary purpose of this chapter is to highlight the recent publications examining the association between PA and breast cancer survival and to discuss the biological mechanisms by which PA might have an impact on outcome/prognosis after a breast cancer diagnosis.

6.2 Physical Activity and Breast Cancer Survival

While multiple observational studies over the past 20 years have demonstrated that women who exercise approximately 3 h.week\(^{-1}\) at a moderate intensity have an approximate 30% decreased risk of developing breast cancer compared to sedentary men and women [2], fewer studies have examined the association between PA after a diagnosis of breast cancer and survival. However, four large observational studies have recently been published demonstrating that participation in moderate-intensity recreational PA after diagnosis is associated with improved survival in women who develop breast cancer [3–6]. These studies have demonstrated a 24–67% reduction in the risk of total deaths and 50–53% reduction in the risk of breast cancer deaths in women who are physically active after breast cancer diagnosis compared with women reporting no recreational PA. These studies also showed that the decreased risk of death associated with PA was observed in pre- and post-menopausal women, overweight and normal weight women, and women with stage I–III disease. These studies are discussed further in Chapter 11.

While any amount of recreational PA performed after diagnosis was associated with a decreased risk of death, the maximal benefit occurred in women who performed the equivalent of brisk walking 3 h.week\(^{-1}\). The type of PA assessed in these studies was sports/recreational PA; however, one study showed similar yet slightly attenuated associations for any moderate-intensity PA (e.g., heavy household work, gardening, occupational activities) [5]. Whilst most of the studies included samples of breast cancer survivors that were professional and primarily non-Hispanic white, one study showed a similar association in African-American and Hispanic women [5]. Given that women who are more physically active after diagnosis may have been similarly active before diagnosis, these studies cannot exclude the possibility that physically active individuals who develop breast cancer acquire tumors that are biologically less aggressive. Therefore, being physically active prior to diagnosis may have been associated with a later diagnosis of breast cancer or earlier disease stage. Two studies, assessing PA in the year prior to diagnosis, observed nonsignificant reduced risks of breast cancer death with higher levels of pre-diagnosis PA [4, 5]. These findings emphasize the importance of participating in PA after a diagnosis of breast cancer to gain the maximum benefits of PA on survival. Lastly, one study examined whether the influence of PA on survival differs according to time since
breast cancer diagnosis, with PA appearing to be beneficial in both early and late post-diagnostic time periods [4].

In summary, these observational findings of post-diagnosis PA and improved survival suggest that exercise may confer additional improvements in breast cancer survival beyond surgery, radiation, and chemotherapy. However, despite this growing body of observational evidence suggesting a strong link between PA and breast cancer survival, there is still the potential for confounding by unknown or poorly characterized variables. For example, PA may be a marker of overall health behaviors including adherence to adjuvant treatments. Thus, RCTs testing the effects of PA on cancer survival and/or surrogate/biological markers or mechanisms mediating the association between PA and survival are necessary and would provide critical information for women about whether and how much lifestyle change can affect their prognosis. While a trial of PA on breast cancer survival has yet to be conducted, a small number of randomized trials of exercise on surrogate/biological markers of survival have been published.

6.3 Biological Mechanisms by Which Physical Activity May Impact upon Breast Cancer Survival

Despite the growing body of observational evidence suggesting a link between PA and breast cancer survival, the mechanisms underlying this relationship are poorly understood. A few small RCTs have examined the impact of exercise on surrogate/biological markers of survival. The beneficial effects of PA might be mediated through a reduction in body fat and beneficial changes in metabolic (e.g., insulin) and sex hormones (e.g., androgens and estrogens), growth factors (e.g., IGF-I and associated binding proteins, e.g., IGFBP-3), adipokines (e.g., leptin, adiponectin), and/or inflammation (e.g., CRP). See Fig. 6.1.

6.3.1 Obesity and Weight Gain

Obesity and weight gain are established negative prognostic factors in breast cancer primarily because body fat is an important source of hormones and adipokines. Recent observational evidence indicates that obesity increases the risk of dying from many more cancers, including breast cancer, than has been previously recognized. As an example, in the ACS Cancer Prevention Study II, a longitudinal cohort study, obesity was shown to increase the risk of dying due to numerous cancers [7]. The data for women revealed a two-fold increased risk of breast cancer death, which has been seen in many studies, but a more pronounced association was also observed in severely obese women (BMI $\geq 40$ kg m$^{-2}$), who had an 88% increased risk of cancer death compared with women who were normal body weight (BMI
Fig. 6.1 Hypothesized mechanisms mediating an effect of PA on breast cancer outcomes

These findings revealed that approximately 30–50% of breast cancer deaths among post-menopausal women in the USA can be attributed to being overweight. Similarly, in an analysis of obesity on breast cancer survival in pre-menopausal women, Daling and colleagues reported that women younger than 45 years of age who had invasive breast cancer and a BMI > 25 kg.m\(^{-2}\) were 2.5 times as likely to die of their disease within 5 years of diagnosis compared with women with a BMI < 21 kg m\(^{-2}\) [8]. These findings of an association between obesity and breast cancer death are apparent even after adjustment for stage at diagnosis and the adequacy of treatment.

Epidemiological studies have also shown that weight gain after a breast cancer diagnosis is associated with an increased risk for recurrence and death compared with those who maintain their weight after diagnosis [9]. This is particularly concerning among women treated for breast cancer given that the majority of them gain a significant amount of weight in the year following diagnosis, and a return to pre-diagnosis weight rarely occurs [10]. Analyses from the Nurses’ Health Study showed that weight gain after diagnosis (∼5–10 lbs) was related to approximately 50% higher rates of breast cancer recurrence and death [9]. The findings were especially apparent in women who never smoked, among women with earlier stage disease, or those who were normal weight before diagnosis.

While these findings are intriguing, not all studies have observed an association between obesity or weight gain and prognosis. Caan and colleagues did not observe an association between post-diagnosis weight gain and breast cancer recurrence risk in the first 5–7 years post-diagnosis [11]. However, weight gain may still have adverse affects on overall survival or risk of other new cancers. Thus, questions remain as to whether it is obesity, weight gain, or both, or their predictors (including low PA levels) that cause an increased risk of breast cancer recurrence and death. Obesity may not be associated with poor prognosis after adjusting for PA or risks may be attenuated if overweight/obese cancer survivors participate in an exercise program.
Because surviving cancer is not just about treating the primary cancer, but also about preventing any second cancers for which patients are at risk, striving to prevent obesity is critically important for cancer survivors. One of the primary methods for preventing or treating obesity and weight gain is increasing PA levels. In the treatment of obesity, adding exercise to a calorie-reduction program enhances weight loss, and regular exercise is a powerful predictor of long-term weight maintenance [10]. No randomized trials have examined the effect of weight loss, established via increases in PA, on cancer survival. Such trials are necessary to establish a causal relationship between weight loss and cancer survival and to better understand the mechanisms mediating the relationships among PA, weight loss, and cancer survival. (For example, does PA with or without weight loss improve disease-free survival?)

While aerobic exercise has been associated with favorable changes in body fat, especially intra-abdominal or visceral body fat, in healthy women [12], few trials have examined the effect of exercise on outcomes of body composition, assessed with valid and reliable measures such as DEXA, in breast cancer survivors. Given that a majority of breast cancer survivors are overweight at diagnosis and also at risk of weight gain, decreasing body fat is a priority in this population. In a recent publication, moderate-intensity aerobic exercise, such as brisk walking, performed for approximately 120 min.week\(^{-1}\), was associated with modest, yet favorable changes in body fat in post-menopausal breast cancer survivors [13]. A dose–response effect was also observed with greater decreases in body fat occurring with higher doses of exercise per week. Another recent study investigated a resistance training program on body composition and observed significant decreases in body fat (–1.15% for exercisers vs. 0.23% in controls, \(p = 0.023\)) with a twice-weekly year long resistance training program in pre- and post-menopausal breast cancer survivors [14]. Their observed between-group ESs for changes in body fat were similar to the ESs observed in the aerobic exercise study. This finding is promising because some women may prefer to control weight through aerobic exercise, such as brisk walking, rather than through resistance training or vice versa.

Future studies are needed to investigate different doses and types of exercise on body composition in breast cancer survivors and certain sub-groups, such as women of various ethnic groups and women taking hormone therapies. Also of importance is the timing of exercise, and whether initiating an exercise program immediately after diagnosis is associated with more favorable changes in body composition (e.g., less weight gain) compared to initiating an exercise program after completing initial treatment.

### 6.3.2 Fasting Insulin and Insulin-Like Growth Factor Levels

There has been increasing evidence that high fasting insulin levels strongly increase the risk of breast cancer recurrence and death. Three recent studies have observed
an approximate three-fold increased risk of all-cause mortality among women with high insulin levels, measured approximately 2 years after diagnosis, relative to women with low insulin levels [15–17]. The strong association between fasting insulin levels and breast cancer death has led a number of oncologists and scientists to consider the targeting of insulin as a therapeutic modality in breast cancer, particularly because insulin can be modified by lifestyle and pharmacologic interventions. Therapies to reduce insulin levels in breast cancer survivors could dramatically decrease cancer-related deaths. A lowering of insulin levels by 25% may improve survival by 5%, the same order of magnitude as the beneficial effect of adjuvant chemotherapy.

Similar to insulin, IGF-I has potent mitogenic and anti-apoptotic properties in normal and malignant breast epithelial cells, whereas IGFBP-3 can either stimulate or suppress cellular proliferation by restricting IGF-I’s availability and biological activity [18, 19]. For insulin, some mitogenic effects may be mediated by interaction with IGF-I receptors, as hyperinsulinemia promotes the synthesis and activity of IGF-I. Although the data are not consistent, high levels of IGF-I and low levels of IGFBP-3 have been associated with an increased risk of breast cancer and adverse prognostic factors [20]; however, a study by Goodwin and colleagues found high levels, rather than low levels, of IGFBP-3 predicted distant recurrence of breast cancer in post-menopausal women [21].

These observational data linking insulin and IGFs and breast cancer mortality have led to four small pilot studies evaluating the impact of PA interventions on levels of insulin and other hormones in women diagnosed with breast cancer, with mixed results. Two studies have demonstrated decreased serum insulin levels in breast cancer survivors [22, 23], but two other studies showed no impact of PA upon insulin levels [14, 24].

Specifically, Fairey and colleagues examined the impact of exercise on insulin and IGFs in breast cancer survivors randomized to a thrice-weekly supervised program of 30 min of stationary bicycling for 15 weeks [24]. While participants in their study exercised for 98% of the prescribed exercise sessions, no significant differences between groups were observed for changes in insulin. However, significant differences between groups were observed for changes in IGF-1 (–10.9%) and IGFBP-3 (–8.4%). Similarly, Schmitz and colleagues examined the impact of a twice-weekly resistance training program on insulin and IGFs [14]. While participants also adhered to over 80% of the sessions, there were no exercise effects on insulin, IGF-I, or IGFBP-3.

The results of the two studies that did observe an effect of exercise on insulin levels demonstrate that the recommended level of moderate-intensity aerobic exercise, 30 min on 5 days.week⁻¹, is well tolerated in breast cancer survivors and efficacious in decreasing levels of insulin. Specifically, Ligibel and colleagues observed a 28% reduction in insulin levels in breast cancer survivors randomized to 4 months of twice-weekly resistance training and 90 min.week⁻¹ of home-based aerobic exercise compared to a 3% decrease in insulin levels in breast cancer survivors randomized to the control group [22]. Irwin and colleagues demonstrated that moderate-intensity
aerobic exercise, such as brisk walking, performed on average for 120 min. week\textsuperscript{-1} over 6 months was associated with 30 and 9% between-group differences (i.e., comparing women randomized to exercise vs. usual care) in insulin and IGF-I [23]. Given that both the Ligibel and Irwin studies enrolled sedentary obese breast cancer survivors having higher baseline insulin concentrations compared to the more active and leaner women enrolled in Fairey and Schmitz’s studies (having lower baseline insulin concentrations), exercise may only have a beneficial effect among heavier, less active women, with higher insulin levels. A similar type and dose of weight-bearing aerobic exercise has also been demonstrated to lower insulin but not IGF-I levels in healthy, yet sedentary and obese women [25].

Another important finding of both these studies is that reductions in insulin, IGF-I, and IGFBP-3 were observed without concomitant decreases in body weight or fat. It has been proposed that changes in body fat mediate or modify the change in insulin and IGFs associated with increased PA. However, these studies found that among exercisers who had no change or increased percent body fat, favorable changes in insulin, IGF-I, and IGFBP-3 were still observed. Furthermore, women randomized to usual care who decreased body fat did not experience subsequent reductions in insulin, IGF-I, and IGFBP-3. This indicates that exercise may be necessary to induce reductions in these hormones, with or without fat loss. However, because of the small sub-group analyses, these findings should be interpreted with caution.

Several possible mechanisms might explain the exercise-induced decreases in insulin and IGFs (independent of changes in body fat) including increased post-receptor insulin signaling, increased glucose transporter protein and mRNA, decreased release and increased clearance of free fatty acids, increased muscle glucose delivery, and changes in skeletal muscle composition favoring increased glucose disposal [26]. Given that high insulin levels promote the synthesis and activity of IGF-I via increases in insulin-mediated changes in IGFBP-3 concentrations, decreases in insulin would favorably influence IGF levels.

In summary, as evidence accumulates for a strong association between high levels of insulin and potentially IGF-I and IGFBP-3 and breast cancer death, it becomes increasingly important to identify modifiable factors that decrease insulin and IGF levels. The responsiveness of insulin and IGFs to lifestyle changes, such as PA, is key to novel strategies for improving prognosis. Future trials should include larger sample sizes to elucidate the significance of sub-group findings, including the impact of baseline BMI levels and weight change during the trial and should examine whether an exercise-induced lowering of insulin levels improves survival.

### 6.3.3 Sex Hormones

Obesity, a high insulin level, and altered IGF levels are also associated with a less favorable sex steroid hormone profile [19]. Sex steroid hormones have powerful
mitogenic and proliferative influences and are strongly associated with the development of breast cancer [27]. A number of clinical trials also show that estrogen ablation increases survival following a diagnosis of breast cancer [28, 29]. Changes in sex hormones are perhaps the most consistently cited potential mechanism for the association between PA and breast cancer. The primary mechanism by which PA could influence sex steroid hormones in post-menopausal women is via decreased body fat, a substrate for estrogen and testosterone production, which results in a reduced tissue capability for aromatization of the adrenal androgens to estrogens [30].

Cross-sectional studies show relationships between body fat, PA, and sex steroid hormone concentrations in healthy women and breast cancer survivors. In a subsample of 267 post-menopausal women randomly selected from the Women’s Health Initiative Dietary Modification clinical trial, BMI was positively associated with estrone, estradiol, free estradiol, and free testosterone and negatively associated with SHBG [31]. Total PA was negatively associated with concentrations of estrone, estradiol, and androstenedione.

In the HEAL study, a prospective cohort study following 1,183 women diagnosed with breast cancer, BMI was positively associated with sex steroid hormone concentrations [32]. Specifically, in 505 women diagnosed with breast cancer in the previous year, women with a BMI $\geq$ 30 kg.m$^{-2}$ had 35% higher concentrations of estrone and 130% higher concentrations of estradiol compared with women with a BMI $< 22$ kg m$^{-2}$ (p $< 0.01$). Similar associations were observed for percent body fat and waist circumference. Concentrations of free estradiol and free testosterone were two to three times greater in overweight and obese women compared with lighter-weight women. These cross-sectional associations may, in part, explain the positive associations between obesity, a sedentary lifestyle, and breast cancer risk and prognosis.

To date, only one randomized controlled exercise trial has been published examining the effect of exercise on sex hormone concentrations in healthy women [30]. While the overall effect of exercise was to decrease serum estrogens and androgens and increase SHBG (resulting in lower amounts of free, active estrogens and androgens) in healthy post-menopausal women, a stronger effect was observed among women who lost body fat with exercise compared to women who did not lose body fat with exercise.

Most recently, 6 months of moderate-intensity aerobic exercise significantly decreased testosterone levels and increased SHBG levels in breast cancer survivors [33]. Furthermore, a dose–response effect was observed, in that women who exercised for longer durations at similar intensities experienced more favorable changes in testosterone and SHBG than women who exercised for shorter durations. However, this is the only published trial of exercise on sex steroid hormone concentrations in breast cancer survivors. Therefore more randomized trials are required to determine the effects of PA and weight loss on sex steroid hormone concentrations in this population.
6.3.4 Adipokines

Preliminary *in vitro* and epidemiologic data have also suggested a link between other hormones such as adipokines (e.g., leptin and adiponectin) and breast cancer prognosis [34, 35].

In human breast cancer cell lines, leptin has been observed to be mitogenic and antiapoptotic, increasing cellular proliferation, as well as inducing cellular transformation [36]. Hyperleptinemia is associated with poorer prognostic indicators, such as higher tumor stage and grade as well as negative steroid hormone receptor status [36, 37], but leptin levels have not been clearly shown to have independent prognostic significance. In addition, leptin promotes angiogenesis, which is essential for breast cancer development and progression and can stimulate estrogen biosynthesis by the induction of aromatase activity.

Circulating leptin concentrations are positively correlated with total adipose tissue mass, such that higher BMI is associated with hyperleptinemia [38]. PA may improve breast cancer survival by reducing the obesity-induced endocrine dysfunction of adipose tissue and thus possibly influencing carcinogenesis. To determine whether obesity and PA were associated with leptin levels in breast cancer survivors, Irwin and colleagues analyzed data from a large cohort of breast cancer survivors enrolled in the HEAL Study [38]. Leptin levels were positively related to higher categories of BMI and lower levels of sports/recreational PA among 505 breast cancer survivors.

Associations between adiponectin and breast cancer have also been published recently [34, 39, 40]. Under conditions of obesity, adiponectin biosynthesis is downregulated, and circulating concentrations are reduced. Adiponectin expression is thus inversely related to total adiposity [34]. In human studies, an inverse relationship between circulating adiponectin levels and breast cancer risk in postmenopausal women has been observed even after controlling for the effects of IGF-1, leptin, BMI, and other risk factors which track with both adiposity and breast cancer risk [41]. Also, larger tumors with higher histological grade and poorer prognosis are observed in women with hypoadiponectinemia [34, 40]. Adiponectin has been determined *in vitro* to have anti-atherogenic, anti-inflammatory, and insulin-sensitizing effects and potentially has a protective role in the regulation of angiogenesis and tumor growth [40].

Few trials have examined the effects of PA on leptin or adiponectin in breast cancer survivors. Recently, Irwin and colleagues examined the effect of 6 months of moderate-intensity aerobic exercise vs. usual care on leptin and adiponectin levels in 75 breast cancer survivors [42]. Baseline correlations between leptin, adiponectin, and measures of adiposity were strong and consistent with available literature; however intent-to-treat analyses of the intervention did not result in statistically significant differences in circulating levels of leptin or adiponectin between exercisers and usual care participants. Strengths of this study were that it utilized exercise programs consistent with national guidelines for PA, the intervention was sufficient in duration, and participants were adherent and compliant to the study goals. However, only modest decreases in body fat were observed. Future research must examine the
nature of the relationship between exercise, adiposity, and adipokines in breast cancer survivors and determine whether exercise alone is sufficient to cause favorable changes in these hormones, which are highly correlated to adiposity, or if greater weight loss (with the addition of a low-calorie diet) is necessary to see favorable effects on circulating adipokines.

**6.3.5 Inflammation**

Chronic inflammation has been associated with poor survival for several cancers including breast cancer [43–45]. Pro-inflammatory factors including CRP, TNF-α, and IL-6 have been utilized as surrogate markers for low-grade chronic inflammation and have been linked to cancer through their effects on apoptosis, cell proliferation, angiogenesis, and metastasis [46]. Breast cancer patients have been shown to have elevated concentrations of CRP prior to surgery, and CRP is higher in women with more advanced stage of disease [47]. CRP is also a risk factor for CV disease, for which breast cancer patients have an increased risk following radiation treatment [47]. A recent study showed that TNF-α expression was similar among patients with benign, in situ, and infiltrating tumors but that the actual activity was lowest in benign tumors because of a lack of receptor expression [48]. Serum IL-6 has been shown to be an independent prognostic factor in patients with metastatic breast cancer and to correlate with disease stage and extent of metastasis [49]. There is also some evidence that high IL-6 serum levels predict poor response to chemotherapy [48].

All three inflammatory factors have been shown to correlate with body fat [34]. IL-6 and TNF-α mediate inflammation and the acute phase response and are secreted by a variety of cell types, including adipocytes. It has been suggested that adipose tissue accounts for approximately 25% of systemic IL-6 [50]. CRP is a classic marker of the acute phase response and its production in the liver is stimulated by IL-6 and, to a lesser extent, by TNF-α.

Little is currently known about the effect of PA on CRP, IL-6, and TNF-α in breast cancer survivors. An RCT in post-menopausal breast cancer survivors was carried out using a 15-week exercise intervention consisting of thrice-weekly cycling sessions [51]. No change was found in the production of IL-6 and TNF-α by cultured blood mononuclear cells, i.e., lymphocytes, monocytes, and macrophages. However, cytokine production in culture may not represent actual production in vivo nor does it represent cytokine production from other sources such as adipocytes. In addition, the authors found a marginally significant effect of exercise on CRP concentrations; CRP decreased by 1.39 mg.L⁻¹ in the intervention group and increased by 0.10 mg.L⁻¹ in the control group.

Most recently, an RCT of exercise in breast cancer survivors examined the effects of exercise on plasma levels of the inflammatory cytokines, IL-6, CRP, and TNF-α [52]. Over 6 months, there were no significant differences between the usual
care and exercise group in changes of IL-6, CRP, or TNF-α. One possible explanation for the lack of effect may be because of the modest fat loss observed. If PA’s effects on inflammation are mediated mostly through fat loss, the prescribed intervention may not have achieved the necessary reduction. However, when the intervention group was stratified by adherence (80% of target PA), there was a statistically significant difference in IL-6 change from baseline to 6 months, but not CRP and TNF-α, between the adherence groups. Among women who exercise at least 120 min.week⁻¹, IL-6 levels decreased by 14.3%, while those exercising less had IL-6 levels that increased by 18.5%. These findings, while supportive of an effect of PA on IL-6 concentrations, must be interpreted with caution as this analysis is not based on intent-to-treat principles and women who are adherent may differ from non-adherers in other ways. However, it is noteworthy that adherers and non-adherers had significantly different changes in percent body fat; adherers had a decrease of −1.5% while non-adherers had a decrease of −0.3%. This lends more supportive evidence for an exercise effect that may be mediated by fat loss.

Though very few studies have examined the effect of PA on plasma levels of inflammatory markers in breast cancer survivors, observational studies and trials have been conducted evaluating relationships between inflammatory markers and exercise in other populations. There is observational support for an association, independent of obesity, between PA and plasma IL-6 and CRP, but not TNF-α, in middle-aged healthy men and women [53]. An RCT among pre-menopausal, overweight women who engaged in two sessions per week over 1 year of resistance training intervention resulted in a reduction in plasma CRP concentration, but no change in IL-6 concentration [54]. Another intervention study among nondiabetic lean and obese men and obese male type 2 diabetics employed an intervention of 60 min of aerobic activity 5 times.week⁻¹. The authors found a 0.9 pg.mL⁻¹ decrease in plasma IL-6 levels in both the lean and obese non-diabetics (32 and 15% reductions, respectively) and a 3.2 pg.mL⁻¹ decrease in plasma IL-6 in the diabetic group (a 52% reduction) [55]. This was accompanied by significant reductions in visceral fat and waist circumference, but not BMI or CRP.

The mechanisms by which PA might reduce inflammatory markers are not well elucidated but may include reduction of adipose tissue, release of anti-inflammatory cytokines during exercise, inhibition of TNF-α production, and the effects of skeletal muscle-derived IL-6 [56]. Body fatness is the most important known determinant of CRP, probably due to the fact that adipose tissue expresses and releases IL-6, inducing hepatic CRP production. In addition, CRP may also be decreased through other mechanisms including increased insulin sensitivity.

In conclusion, large scale trials with breast cancer survivors should examine the effect of different types and intensities of PA on inflammatory markers and should aim to determine whether certain variables, such as body fat loss, modify the potential effect of exercise on inflammatory markers. In addition, these studies should assess the effect of PA and inflammatory markers on patient outcomes, including clinical end-points such as disease recurrence and survival.
6.4 Other Potential Mechanisms Mediating an Effect Between Physical Activity and Breast Cancer Survival

Cancer and its treatment are associated with pronounced immune deficiency, and blood immune function is positively associated with survival [57]. The immune system is thought to play a role in protecting against breast cancer by recognizing and eliminating abnormal cells. Changes in immune function may mediate the relationship between PA and breast cancer prognosis. A growing literature on small exercise intervention studies shows that PA improves immune function, including increased natural killer cell cytotoxic activity, monocyte function, and the proportion of circulating granulocytes [58]. Fairey and colleagues reported the effects of a randomized controlled exercise trial on changes in cell-mediated immune function in 52 post-menopausal breast cancer survivors [59]. They found that exercise training evoked an increase in NK cell cytotoxic activity (6.5%) and unstimulated $[^{3}\text{H}]$ thymidine uptake by peripheral blood lymphocytes. Exercise-induced modulation of blood immune function is biologically plausible. Physiological mechanisms that may explain the changes in NK cell cytotoxic activity and $[^{3}\text{H}]$ thymidine uptake by peripheral blood lymphocytes include changes in neuroendocrine status, hematopoiesis, leukocyte apoptosis, muscle damage, protein synthesis, glucose metabolism, and antioxidant defenses [59]. Future research needs to examine whether differential effects are evoked by altering the dose (frequency, intensity, duration) or type of exercise in breast cancer survivors.

Lastly, reactive oxygen species (i.e., free radicals) can play a significant role in breast cancer via their ability to cause DNA damage, as well as damage to other cellular components which interact with DNA. Acute exercise may promote free radical production while chronic exercise improves free radical defenses by up-regulating both the activities of key free radical scavenger enzymes and levels of antioxidants [59]. To date, no studies have examined reactive oxygen species-related damage or relevant antioxidant enzymes in the context of exercise in a cancer model.

6.5 Summary and Conclusions

With numerous publications showing statistically and clinically significant associations between obesity, fasting insulin levels, sex steroid hormones, and breast cancer recurrence and death, more effective treatment strategies to reduce body fat, insulin, and sex steroid hormone levels in breast cancer survivors should be explored. Although considerably more research is needed to determine the effect of PA on these biological markers, we posit that PA decreases breast cancer death directly and indirectly through multiple, interrelated actions of body fat levels and/or hormonal concentrations and actions.

In terms of breast cancer survival, many questions need to be answered concerning who would benefit from increasing PA, when PA would be most beneficial, and how much PA would be optimal. Given the high levels of physical inactivity in the
population, and the heavy burden that breast cancer creates for the individual and for the society, the need for well-designed trials of exercise on breast cancer survival, and surrogate/biological markers mediating a potential effect, is an urgent public health priority.

References

Chapter 7
Exercise After Prostate Cancer Diagnosis

Daniel Santa Mina, Paul Ritvo, Roanne Segal, N. Culos-Reed, and Shabbir M.H. Alibhai

Abstract  PCa is the second most commonly diagnosed cancer in men. Though often curable or treatable with an excellent long-term survival, many therapeutic options reduce health-related QoL. Exercise and regular PA have been demonstrated as beneficial throughout the continuum of the disease. Clinically important benefits have been observed particularly during the active treatment phase. Several recent intervention trials have investigated the effects of different exercise modalities (e.g., aerobic exercise, resistance training) during treatment on patient health-related QoL with promising results. Given the observed benefits, the issue of exercise adherence is becoming the focal point of studies as researchers strive to initiate a chronic health behavior change of increased PA to maintain exercise benefits beyond the acute intervention phase. This chapter reviews the current body of literature on exercise during PCa treatment and provides recommendations for future studies, implications for clinical practice, and preliminary recommendations for exercise prescription.

7.1 Introduction

PCa is the most common cancer diagnosis in North American men and the leading cause of cancer death in men over 70 years [1, 2]. PCa typically affects men in their senior years, with a mean age at diagnosis of 68–70 years [1, 2]. The incidence of PCa is increasing worldwide, with the highest rates found in North America [3]. Rising incidence rates over the past two decades have been partially attributed to more diagnoses of incidental cancers as a result of increases in TURP, PSA screening, and because of the “westernization” of lifestyles (e.g., high-fat diet and low levels of PA) in previously low-risk Asian populations [4]. Simultaneously, 5-year disease-specific survival rates for men with newly
diagnosed PCa now approach 100%, likely because of earlier stage at diagnosis and therapeutic advancements such as improved surgical techniques, and targeted dose-escalated RT [1–3].

7.1.1 Screening

PCa screening typically includes routine DRE and PSA screening for men over the age of 50 years. PSA is produced by the epithelial cells of the prostate gland and levels may be elevated in normal prostate tissue, in BPH, in PCa localized to the prostate gland, and in metastatic lesions. Serum PSA is useful in PCa diagnosis despite the fact that its fluctuations are not cancer specific. In addition to screening, PSA is an important tool for staging PCa and for treatment decision making. PSA has been shown to correlate with increasing stage, tumor volume, and pathological stage.

Patients with palpable nodules on DRE or PSA values >3–4 ng.dL⁻¹ (>3–4 mg.L⁻¹) subsequently undergo prostate biopsies for confirmation of diagnosis, tumor staging, grading, and treatment planning. PCa-screening improvements have contributed to the vast majority of men (85–90%) being diagnosed with early stage disease, i.e., cancer confined to the prostate gland.

7.1.2 Tumor, Node, Metastasis Staging

The TNM staging system for PCa is traditionally used to clinically define the volume and extent of cancer. The primary tumor (T) stage ranges from 1 to 4: in stage T1, the tumor is non-palpable; in stage T2, the tumor is confined to the prostate gland; in stage T3, the tumor extends beyond the prostatic capsule; and in stage T4, the tumor has directly spread beyond the adjacent tissues. Nodal disease (N) is evaluated in terms of the presence of malignancy in the regional and distant lymph nodes and may be detected by radiological evaluation or subsequent to RP. The M component of staging refers to the absence or presence of disease outside the regional prostate gland and nodes (i.e., metastases), with the most common sites of spread being the bones (~80%) and/or the retroperitoneal lymph nodes.

7.1.3 Histopathological Grading

A histological grade is traditionally assigned using the Gleason scoring system that is based on the heterogeneity of prostatic carcinomas, describing different patterns of malignant growth. The two most common microscopic patterns observed in the tissue specimen, noted as primary and secondary, are each identified and scored (a scale of 1–5, from well-differentiated to poorly differentiated). A composite
Gleason sum ranging from 2 to 10 is based on the sum of the two most common patterns.

### 7.1.4 Treatment

For treatment purposes, PCa is broadly categorized into three stages: (1) *early stage* (further divided into low, intermediate, and high risk based on tumor stage, Gleason score, and PSA level (Table 7.1)), (2) *locally advanced* (Stage T3–4; N+), and (3) *metastatic disease*. Metastatic PCa can be further divided into *hormone-sensitive* and *hormone-refractory* disease. Prostate cells, both benign and cancerous, depend on androgens (male sex hormones) for growth. ADT is thus commonly used to suppress androgen production and slow tumor growth. Metastatic PCa that is hormone-sensitive is either seen on initial presentation or, more commonly, after initial treatment failures. Metastatic PCa that progresses despite androgen suppression is identified as hormone refractory.

<table>
<thead>
<tr>
<th>Pathological variable</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor stage</td>
<td>T1 or T2a</td>
<td>T2b</td>
<td>T3, T4</td>
</tr>
<tr>
<td>Gleason score</td>
<td>≤6</td>
<td>7</td>
<td>8–10</td>
</tr>
<tr>
<td>PSA level</td>
<td>&lt;10</td>
<td>10–20</td>
<td>&gt;20</td>
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<tr>
<td>Usual treatmenta</td>
<td>EM, EBR, BT, or RP</td>
<td>EBR, BT, or RP</td>
<td>EBR or RP with adjuvant ADT</td>
</tr>
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PSA = prostate-specific antigen; EM = expectant management; EBR = external beam radiation; BT = brachytherapy; RP = radical prostatectomy; N+ = lymph node metastasis.

*a*Usual treatment includes treatment options typically recommended for patients who are in otherwise good health and have a reasonable remaining life expectancy.

In early stage disease, treatment is contingent on the risk classification of the cancer (Table 7.1), in combination with the patient’s estimated remaining life expectancy, and co-morbidities (including urinary and sexual function) [5]. Three primary management options are available: RP, RT, and EM. For high-risk and metastatic patients, or for patients ineligible for RP or RT, ADT is often used.

RP involves complete surgical removal of the prostate gland and surrounding tissues. The common complications of erectile dysfunction and urinary incontinence may negatively impact health-related QoL and persist for years [6–9]. A number of patients also experience pain and/or decreased energy that may persist for 1–2 years or longer.

RT consists of EBR or BT and is often a treatment option used for low- or intermediate-risk PCa. EBR is also used to treat early stage high-risk disease. EBR sometimes affects the surrounding or normal tissues during treatment, leading to side effects such as fatigue, erectile dysfunction, urinary incontinence, and bowel complications. BT (also known as seed implants or interstitial therapy) involves
implantation of radioactive seeds (iodine-125 or palladium-103) directly into the prostate gland. BT may be associated with fewer side effects than EBR [10].

EM, also known as “watchful waiting,” is a strategy generally reserved for men with low-risk disease and/or limited life expectancy, particularly when the benefits of localized treatment appear to be outweighed by probable treatment-related morbidities. In the EM paradigm, men only receive treatment with disease progression. More recently, AS has emerged as an alternate option to EM, and incorporates close, regular monitoring of disease via PSA, DRE, and routine prostate biopsies. Appropriate treatment (RP, RT, ADT, or combinations of treatment) is recommended if there is evidence of disease progression on routine monitoring. AS avoids upfront treatment-related morbidities but requires ongoing commitments to clinic visits and serial testing [11, 12]. This therapeutic strategy is currently being investigated in a large randomized clinical trial among patients with low-risk PCa [13]. However, at present, there are no completed randomized trials of AS compared to standard treatment options, and long-term outcome data are also limited.

ADT (also known as androgen suppression, hormone ablation, or hormone therapy) was once the standard of care in men with hormone-sensitive PCa. However, it is now widely used in the neo-adjuvant (prior to RT), adjuvant (post-RT or RP), and hormone-sensitive metastatic settings. In a neo-adjuvant (i.e., prior to definitive treatment) setting, ADT is used to reduce the burden of malignant cells prior to RT [14–16]. In patients who present with high-risk or locally advanced disease, ADT is usually added to RP or RT (adjuvant therapy) to prolong survival and is continued for 2–3 years.

Patients with metastatic disease starting ADT will remain on therapy for as long as there are clinical benefits (e.g., improved health-related QoL). While this period, on average, lasts 18–24 months, therapy may be effective for a decade or more. The physical, functional, and psychological detriments that are associated with ADT are due to prolonged periods of hypogonadism, which causes reductions in Hb, BMD, lean body mass, and increases in fat mass [17–24]. These side effects collectively reduce health-related QoL [25–31].

Chemotherapy may be indicated for men with hormone-refractory disease, particularly if symptomatic. Docetaxel and prednisone constitute the standard cytotoxic chemotherapy regimen and are associated with improved survival, pain response, PSA response, and health-related QoL compared to a more palliative regimen of mitoxantrone and prednisone, or no therapy [32, 33]. Side effects of docetaxel include bone marrow suppression, neuropathy, myalgia, and fatigue [32, 34].

Each conventional PCa treatment modality is associated with a constellation of acute and chronic side effects that may negatively impact functional, physical, emotional, and social aspects of health-related QoL. Several of these treatments are also commonly associated with significant fatigue. Given the trend toward earlier diagnosis and interventions, along with excellent 10-year survival, men must cope with such side effects for longer durations. Accordingly, clinicians and researchers have been challenged to develop comprehensive treatment programs to optimize peri- and post-treatment health-related QoL, many of which now incorporate exercise modalities.
7.2 Exercise and Prostate Cancer Prevention

While much remains to be clarified about the protective role of PA in PCa prevention, reviews of PCa risk and (PA) participation indicate that most studies demonstrate risk reductions, although some positive (i.e. adverse) dose–response relationships between PA and PCa incidence have been observed [40, 41]. Despite such inconsistencies, the collective evidence indicates a “probable” but modest risk reduction in PCa for the most active men versus the least active [40, 41]. For example, the Health Professionals Follow-up Study prospectively followed 47,620 male health professionals from 1986 to 2000, and although no association between non-vigorous, vigorous, and total PA with total PCa incidence was detected (among men aged 65 years and older), the highest category of PA (> 29 MET-h.week\(^{-1}\) or approximately 3 h of vigorous PA weekly) was associated with a significantly lower risk of incident high-grade PCa (Gleason 7 or higher), advanced CaP (RR = 0.33, 95% CI = 0.17–0.62), and fatal PCa (RR = 0.26, 95% CI = 0.11–0.66) [42].

While no research has investigated the effects of exercise on clinical outcomes and survival in patients selecting EM or AS, \textit{in vitro} studies have demonstrated reduced LNCaP in men adhering to short-term or long-term exercise combined with healthy diet regimens [43, 44].

7.2.1 Mechanisms of Prevention

Hypothesized biological mechanisms for protective exercise effects include modified hormonal functions, reduced body fat, and enhanced immune and antioxidant function [40, 45]. A series of studies investigating the effects of a low-fat diet and/or regular PA have suggested that these healthy lifestyle modifications can elicit serum changes \textit{in vivo} that can reduce proliferation and increase the apoptosis of androgen-dependent cell lines \textit{in vitro} [43, 44, 46–48]. The protective effects in these studies are likely due to the reductions in insulin and IGF (e.g., IGF-1) and anti-apoptotic proteins (Bcl-2), amidst concomitant increases in sex hormone-binding globulin, IGFBP-1, and apoptotic proteins (p53 and p21) [47, 49, 50]. Theoretical concerns of accelerating tumor growth due to transient increases in serum testosterone levels have not been found in several exercise studies with PCa patients [51–53]. Moreover, hormone-sensitive PCa cells (LNCaP) appear more susceptible to apoptosis and reduced proliferation in a medium of serum affected by acute and chronic exercise along with healthy diets [43]. Collectively, these studies suggest the impact of exercise on PCa likely extends beyond the pre-diagnosis stage and into the treatment and recovery phases.

Despite this array of apparently anti-carcinogenic effects, preliminary unpublished data from a recent study demonstrated significantly greater tumor growth in exercising compared to sedentary mice [54]. While worth noting, these findings remain controversial, as they have not been demonstrated in human studies. Further studies and multiple attempts at replication in mice and humans are necessary before a full evaluation can be undertaken.
7.3 Exercise Post-diagnosis of Prostate Cancer

A growing number of studies have investigated the effect of exercise during PCa treatment. All of them have yielded positive results, providing optimism for the use of exercise in improving health-related QoL. As previously noted, exercise has become increasingly recognized as an innovative addition to existing treatment paradigms in optimizing health-related QoL throughout treatment. This is particularly critical as PCa patients appear vulnerable to a variety of health-related QoL-reducing symptoms associated with treatment. One systematic review of PA in PCa survivors has been conducted and included 16 studies that assessed the outcomes, prevalence, and/or determinants of PA in this population [55]. Six intervention studies that investigated outcomes of PA among PCa survivors were assessed, and all of them demonstrated improvements in muscular fitness, fatigue, and physical functioning, with three of the four studies that measured global health-related QoL showing significant, positive results. Furthermore, all studies demonstrated that PA was safe for PCa patients undergoing treatment.

Despite this growing body of research, exercise is rarely discussed and infrequently incorporated into standard PCa treatment [56, 57]. This may be due, in part, to the absence of standardized exercise guidelines. The following review of exercise interventions for PCa patients will help in directing further research and deriving clinical exercise recommendations that can overcome this unfortunate gap in clinical care (see Table 7.2 for a summary of all published exercise trials in PCa).

7.3.1 Exercise for Early Stage, Localized Disease

For PCa patients with early stage, localized disease, the data on prevention reviewed above suggest a possible beneficial role for exercise in slowing the progression of primary tumors. However, there are no data specifically examining exercise effects on PCa tumor growth in animals or humans. Exercise may also play a role in a neo-adjuvant setting, preparing patients to undergo therapy by reducing adiposity (see Section 5.1.1) and/or improving CV health. The following sections describe the current evidence relating to exercise within different treatment settings for early stage, localized PCas.

7.3.1.1 Radical Prostatectomy

For patients who opt for RP, improvements in pre-operative fitness and body composition may have positive effects on treatment outcomes, especially if improvements involve weight loss, as excess abdominal adiposity increases treatment risks. For example, excess abdominal adiposity may increase operative complexity, blood loss,
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<tr>
<td><strong>Interventions for PCa patients treated with EBR</strong></td>
<td><strong>N = 66 PCa patients treated with EBR; n = 51 had early stage tumors (T1–T2); n = 19 were treated with adjuvant (ADT); mean age = 68.8 years</strong></td>
<td><strong>RCT: home-based exercise (n = 33) versus standard care control (n = 33)</strong></td>
<td><strong>Minimum of three sessions weekly for 4 weeks, unsupervised, home-based walking at 60–70% of estimated MHR for 30 min</strong></td>
<td><strong>Participation rate = 86% (n = 11 refused); Adherence rate = 100% (all patients in the exercise group recorded at least 90 min.week⁻¹ of AE at the recommended HR)</strong></td>
<td><strong>BFI, modified shuttle walking test, RHR, exercise HR</strong></td>
<td><strong>Control group: increased fatigue scores from baseline to treatment completion (p = 0.013), stable fatigue symptoms in the exercise group (p = 0.203); greater walking distance for the exercise group compared to the controls (p = 0.0025)</strong></td>
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Table 7.2  Exercise trials in PCa
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<tr>
<td>Monga et al.</td>
<td>$N = 21$; localized PCa treated with EBR; mean age of AE</td>
<td>RCT: AE ($n = 11$) versus control ($n = 10$)</td>
<td>Three sessions weekly for 8 weeks, supervised, facility-based walking at 65% of HRR for 30 min plus 5–10 min of warm-up and cooldown</td>
<td>Participation rate = 60%; adherence rate not reported</td>
<td>Bruce treadmill test; MSR; stand and sit test; PFS; FACT-P; BDI</td>
<td>Compared to controls, the intervention groups experienced significant improvements in CV fitness ($p = 0.006$), lower extremity strength ($p = 0.000$), flexibility ($&lt;0.01$), fatigue ($p &lt; 0.001$), physical well-being ($p &lt; 0.001$), social well-being ($&lt;0.002$), functional well-being ($p = 0.04$), and overall health-related QoL ($p = 0.006$)</td>
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<tr>
<td>Segal et al. 52</td>
<td>N = 121 PCa patients treated with EBR; n = 74 treated with adjuvant ADT; (n = 96 subjects had stage I or II disease; n = 22 had stage III or IV disease; n = 3 had unassigned disease staging) mean age 66.3</td>
<td>RCT: RT (n = 40) versus AE (n = 40) versus wait-list controls (n = 41)</td>
<td>Three sessions weekly for 24 weeks, supervised, facility-based AE or RT for 15–45 min</td>
<td>Participation rate = 37%; adherence rate = 75.9%</td>
<td>FACT-F; FACT-P; FACT-G; PSA; testosterone; Hb; serum lipids (total cholesterol, LDL, HDL, triglycerides); upper and lower body muscular strength test; O2 max (ramp protocol)</td>
<td>RT improved fatigue (p = 0.007), aerobic fitness (p = 0.034), upper (p &lt;0.001) and lower (p &lt; 0.001) body fitness, and body fat percentage (p = 0.029). Compared to controls, AE improved aerobic fitness (p =0.047) and body fat percentage (p = 0.033); trend toward improved fatigue (p = 0.060); trend of RT superior to AE in aerobic fitness</td>
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<td>Interventions for PCa patients treated with ADT</td>
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<td>Three sessions weekly for 12 weeks, supervised, facility-based RT at 60–70% of 1 RM for two sets of 10–12 repetitions</td>
<td>Participation rate = 30.6%; adherence rate = 79%</td>
<td>FACT-F; FACT-P; standard load upper and lower body strength test; body weight, BMI, WC, subcutaneous skinfolds</td>
<td>RT subjects reported less fatigue ($p = 0.002$), higher HQL levels ($p = 0.001$), better upper ($p = 0.009$), and lower ($p &lt; 0.001$) body muscular fitness</td>
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<td>Segal et al. [51]</td>
<td>$N = 155$ PCa patients treated with ADT; $n = 75$ with stage I or II disease; $n = 51$ with stage III or IV disease; $n = 29$ had unassigned disease staging; mean age 67.9 years</td>
<td>RCT: RT program ($n=82$) versus a waiting list control group ($n=73$)</td>
<td>RT program consisted of nine upper and lower body exercises (leg extension, leg curl, seated press, lat pull-down, overhead press triceps extension, bicep curls, and modified curl-ups)</td>
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<td>Galvao et al.</td>
<td>N = 11; PCa patients treated with ADT (n = 5 on acute ADT ≤ 12 months; n = 6 on ADT &gt; 12 months; mean duration = 1135.6 days)</td>
<td>Uncontrolled trial; pre/post-test</td>
<td>Two sessions weekly for 20 weeks of supervised, facility-based RT (6–12 RM for two to four sets) for 60 min session⁻¹</td>
<td>Participation rate = (91 subjects approached, n = 10 refused, n = 13 eligible, n = 67 ineligible); adherence rate = (n = 1 dropout; otherwise not reported)</td>
<td>1 RM; muscle endurance test (maximum number of repetitions at 70% of 1 RM); chair rise to standing; 6-m walk; 6-m backward walk; stair climb; 400-m walk; sensory organization test; DEXA, B-Mode ultrasound, Hb, PSA, testosterone, GH, and cortisol</td>
<td>Pre–post-improvements in: upper body strength and endurance (p &lt; 0.001); functional performance (p &lt; 0.05); quadriceps muscle thickness (p &lt; 0.05)</td>
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<td>Carmack-Taylor et al.</td>
<td>$N = 134$; PCa patients treated with ADT (mean duration of ADT = 32.7 months); mean age 69.2 years</td>
<td>RCT: lifestyle program ($n = 46$) versus educational support group ($n = 51$) versus standard care ($n = 37$)</td>
<td>Monthly group-based sessions for 6 months to increase unsupervised PA to 30 min of moderate intensity exercise for most days per week. To facilitate PA adherence, subjects were taught cognitive-behavioral and exercise monitoring strategies</td>
<td>Participation rate = 22%; adherence rate = 64%</td>
<td>SF-36, CES-D, STAI, BPI, 6-min walk test, BMI, WC, HC, WHR, ISEL, 7-DPARQ, the stage motivational readiness for PA, processes of change for PA questionnaire, decisional balance for PA; self-efficacy questionnaire</td>
<td>No significant effects were found in any of the outcome measures</td>
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<tr>
<td>Culos-Reed [77]</td>
<td>$N = 31$; PCa patients treated with ADT for a minimum of 6 months; mean age = 64.8</td>
<td>Uncontrolled trial; pre/post-test</td>
<td>Three to five sessions.week$^{-1}$ for 12 weeks, unsupervised, home-based mixed modality exercise 90-min “Booster Sessions” held at 2-week intervals for group exercise, and to discuss progress, concerns, and foster/monitor adherence</td>
<td>Participation rate = 53% adherence rate = 81% of participants attended five or six of six offered booster sessions</td>
<td>GLTEQ – LSI; RHR; 6-min walk test; hand-grip dynamometer test; MSR; EORTC-QLQ C30; FSS; BMI</td>
<td>Pre–post-intervention improvements in strenuous/total PA ($p &lt; 0.01$) and functional capacity ($p &lt; 0.01$), resting HR ($p = 0.03$), BMI ($p &lt; 0.01$), and fatigue ($p = 0.05$) At 4 months post-intervention ($n = 18$): decreased strenuous PA ($p = 0.01$) and health-related QoL ($p = 0.04$)</td>
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<td>Culos-Reed et al.</td>
<td>N = 100 PCa patients receiving ADT for a minimum of 6 months, intervention group mean age = 67.2, control group mean age = 68 years</td>
<td>RCT: mixed modality exercise (n = 53) versus wait-list control group (n = 47)</td>
<td>Three to five sessions weekly for 16 weeks of unsupervised, home-based mixed modality exercise, home-based intervention 90-min “Booster Sessions” held each week during intervention, and then monthly to the end of follow-up. Each session was designed to foster/monitor adherence and consisted of group exercise, and Discussion regarding progress and concerns</td>
<td>Participation rate = not reported; adherence rate = 77.8%</td>
<td>EORTC QLQ-C30; EPIC; FSS; CES-D; GLTEQ-LSI; RHR, BP, 6-min walk test, hand-grip dynamometer test, modified sit and reach, weight, BMI, WC, HC, WHR</td>
<td>Intervention improved PA levels (p &lt; 0.004), waist girth (p &lt; 0.044), and neck girth (p &lt; 0.019), and hormone symptoms (&lt;0.074)</td>
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7D-PARQ = 7-Day Physical Activity Recall Questionnaire; AE = aerobic exercise; BDI = Beck Depression Inventory; BFI = Brief Fatigue Inventory; BMI = Body Mass Index; BPI = Brief Pain Inventory – short form; CES-D = Centre for Epidemiological Studies – Depression Scale; DEXA = dual X-ray absorptiometry; EORTC-QLQ C30 = European Organization for the Research and Treatment of Cancer 30 Item Core-Quality of Life Questionnaire; EPIC = Expanded Prostate Cancer Index – Composite; FACT-F = functional assessment of cancer therapy – fatigue; FACT-G = functional assessment of cancer therapy – general; FACT-P = functional assessment of cancer therapy – prostate; FSS = fatigue severity scale; GLTEQ-LSI = Godin Leisure Time Exercise Questionnaire – Leisure Score Index; Hb = hemoglobin; HC = hip circumference; HDL = high-density lipoprotein; HR = heart rate; HRR = heart rate reserve; ISEL = interpersonal support evaluation list; LDL = low-density lipoprotein; MHR = maximum heart rate; MSR = modified sit and reach; PA = PA; PFS = Piper Fatigue Scale; PSA = prostate-specific antigen; RHR = resting heart rate; RM = repetition maximum; RT = resistance training; SF-36 = short form 36; STAI = State/Trait Anxiety Inventory; WC = waist circumference; WHR = waist-to-hip ratio.
and blood transfusion requirements and result in higher risks for residual tumor following surgery and disease recurrence [58–60]. The increase in abdominal adiposity may also lead some surgeons to operate more quickly to reduce blood loss, reducing the time that can be spent on preserving the nerves that contribute to erectile and urinary function. Furthermore, abdominal fitness and better muscular definition may improve the surgeon’s ability to dissect through the local musculature, possibly expediting recovery and reducing post-operative discomfort. Unfortunately, no studies have yet been conducted to investigate the effects of a pre-operative exercise intervention on post-operative clinical or psychosocial outcomes after RP.

### 7.3.1.2 Radiation Therapy

There have been three published trials investigating the effect of exercise on PCa patients undergoing RT. Windsor et al. [61] conducted an RCT focused on the effects of a home-based, moderate intensity, walking program on PCa patients (n = 66) undergoing EBR over 4 weeks of treatment. Patients in the intervention group were instructed to exercise three times weekly for 30 min at 60–70% of the MHR. Controls experienced significant worsening in fatigue from baseline to the end of 4 weeks of treatment, while fatigue scores remained unchanged for the exercise group. Superior physical functioning was observed in the exercise group when compared to controls. A 100% adherence rate was noted, as all patients in the exercise group reported at least 90 min.week⁻¹ of aerobic exercise. The excellent adherence rate is promising, although further studies with long-term follow-up are needed to demonstrate reproducibility and sustainability.

Monga et al. [62], conducted an RCT to examine the effects of an 8-week aerobic exercise program in 21 men undergoing EBR for localized PCa. Intervention subjects (n = 11) were required to participate in supervised aerobic exercise three times weekly for 8 weeks, prior to treatment. The exercise protocol included 30 min of treadmill walking at moderate intensity. Exercise participants experienced improvements in CV fitness, lower extremity strength, flexibility, fatigue, physical well-being, social well-being, and overall health-related QoL in relation to baseline measures and control patients. This was the first study to demonstrate improvements in fatigue and health-related QoL with a supervised, aerobic exercise program for PCa patients undergoing RT. Caution is required in interpreting results because of small sample size, selection bias, and retention difficulties (approximately 20% dropout). Adherence to the supervised exercise sessions was not reported.

More recently, Segal et al. [52] conducted a three-arm RCT of 121 RT-treated PCa patients (n = 74, 61.2% of whom were also receiving ADT) comparing 24 weeks of supervised resistance training versus 24 weeks of supervised aerobic exercise versus wait-list controls. Subjects in the aerobic exercise group exercised three times weekly at a moderate intensity on a cycle ergometer, treadmill, or elliptical machine for 15–45 min. Subjects in the resistance training group performed nine resistance exercises using weight machines and free weights. These subjects were expected to train three times weekly with one to two sets of 8–12 repetitions
for nine exercises at 60% of the subject’s one repetition maximum load (1 RM: the maximal weight or load that can be lifted once). Participants were instructed to increase exercise resistance by 5 lbs (2.3 kg) when able to complete more than 12 repetitions. Results demonstrated an improvement in fatigue from baseline to 12 weeks for both aerobic and resistance training groups compared to usual care, but only the resistance training group demonstrated improved fatigue compared to usual care at 24 weeks. From baseline to post-test, the resistance training group experienced improved aerobic fitness and upper/lower body strength, while subjects in the aerobic exercise group demonstrated improved upper body strength. A recruitment rate of 37% was noted for all eligible participants and the median adherence to the exercise program was 85.5%. The only medically confirmed adverse event was an acute myocardial infarction in the aerobic exercise group on the third day of the training protocol and the patient made a full recovery.

In a supplemental analysis, Segal et al. [52, supplemental material] examined the effect of their exercise intervention on PCa patients at 24 weeks, stratified by treatment (EBR ± ADT). Compared to control subjects, the resistance training group on EBR only (n = 23) demonstrated significant improvements in: fatigue, cancer-related and disease-specific health-related QoL, $\dot{V}O_2$peak, and upper and lower body strength. The aerobic exercise group of men receiving only EBR (n = 25) only showed improvements in disease-specific health-related QoL. Among men receiving adjuvant ADT, resistance training (n = 17) improved upper and lower body strength, and reductions in body fat percentage, whereas aerobic exercise (n = 15) only improved upper body strength when compared to controls. Although this analysis is exploratory and lacks adequate statistical power, the data suggest that resistance training appears to be more beneficial than aerobic exercise for men treated with EBR.

There are no studies of exercise for PCa patients undergoing BT or EM. Despite temptations to extrapolate the beneficial impacts of exercise from EBR to other treatment modalities, it is noteworthy that each treatment can be associated with specific health-related QoL decrements that fluctuate during and after treatment. Thus, each treatment modality should optimally be tested in RCTs to assess the health-related QoL impact and the safe parameters in which exercise can be implemented.

### 7.3.2 Exercise for Locally Advanced and Hormone-Sensitive Metastatic Disease

While the findings above are promising, the majority of research on exercise and PCa has been conducted in patients with locally advanced or hormone-sensitive metastatic disease treated with ADT. Given the detrimental effects of ADT on physical function and fatigue from prolonged hypogonadism, exercise offers a treatment option that can lessen some of these negative effects. Fatigue is particularly prevalent in patients who undergo chronic (greater than 1 year) ADT and may have several potential underlying physiological mechanisms. Anemia likely results from inhibition of erythropoiesis through direct androgen suppression [21] or may result
from reduced erythrocyte production of bones at metastatic sites (vertebral bodies, pelvis, and long bones) [63]. Moreover, fatigue may be exacerbated through reductions in CV function, muscular efficiency, strength, and endurance, as well as changes in the androgen receptor complex and endocrine regulation (e.g., IGF-1 and growth hormone) [64]. ADT also negatively impacts upon physical function, possibly through reductions in lean muscle mass, and the neuromuscular pathways that affect strength and dexterity. A recent study by Soyupek et al. [30] compared 20 patients with locally advanced PCa on ADT to healthy aged-matched controls and found that grip strength and hand dexterity were worse in ADT users. Clay et al. [65] found that compared to controls, men on chronic ADT had significantly slower walking speed and lower extremity function. Furthermore, preliminary results from a prospective cohort study conducted by Breunis et al. [66] suggest that endurance and upper extremity physical function are reduced within 3–6 months of ADT initiation compared to both PCa patients not on ADT and healthy controls. Potosky et al. [67] demonstrated that these physical limitations are clinically meaningful, in that men who were treated for high-risk PCa had significant reductions in their abilities to complete daily activities, when compared to men not receiving treatment. Collectively, these physiological and functional side effects may contribute to the elevated fracture risk seen in this population [18–20, 28, 68–70] that is, in turn, negatively associated with survival [71]. Exercise, specifically resistance training, has demonstrated a beneficial impact on acute physical function and may prove to have long-term benefits for preventing osteoporosis and fractures.

Segal et al. [51] conducted the first study investigating the effects of resistance training on PCa patients scheduled to receive ADT for at least 3 months. In this study, 155 men were randomly assigned to a 12-week supervised exercise program ($n = 82$) or to a wait-list control group ($n = 73$). The resistance training program consisted of nine exercises targeting upper and lower body muscle groups, performed three times weekly, at 60–70% of 1 RM, for two sets of 10–12 repetitions. Participants increased the resistance of an exercise by 5 lb (2.3 kg) when able to complete more than 12 repetitions. Results indicated that intervention subjects reported less fatigue, higher levels of health-related QoL, and better scores on measures of upper and lower body muscular fitness, than controls. In fact, control subjects reported increases in fatigue and declines in health-related QoL as well as upper and lower body muscular fitness. Participants attended 79% of the exercise sessions provided, demonstrating the willingness and motivation to comply with intervention requirements. This landmark study provided two salient findings for patients on ADT: (1) clinically important improvements in physical function, fatigue, and health-related QoL are attainable within a relatively short duration of exercise programming and (2) physical inactivity was associated with physical function declines that possibly increased fatigue and reduced health-related QoL.

Following the Segal et al. study, Galvao et al. [53] examined the effects of a 20-week supervised progressive resistance training program in 10 men undergoing ADT for localized PCa. Patients were required to be on ADT for a minimum of 2 months with at least 5 months of subsequent treatment planned. In small groups ($n = 1–4$) and under direct supervision, participants were expected to complete 12
upper and lower body exercises. All exercise sessions were kept to 1-h duration, including flexibility training and warm-up. Results showed improvements in upper body strength and endurance, functional performance, and quadriceps muscle thickness. No differences were found in body composition (lean mass, fat mass, body fat percentage), whole body bone mineral content, or BMD, circulating Hb, or cortisol. PSA level, testosterone, and growth hormone were unchanged suggesting no exacerbation of the disease. Limitations to this study include a non-randomized, no-control experimental design, small sample, and varying durations of ADT (although all participants were undergoing ADT throughout the course of program participation). Strengths include use of several additional objective measures of functional performance and, as advocated by Segal and colleagues, sophisticated measures of body composition and serological outcomes (e.g., hormones and Hb).

Carmack-Taylor et al. [72] conducted a three-armed RCT named the Active for Life After Cancer Trial that evaluated the impact of a group-based lifestyle PA program (Lifestyle Program) or educational support program versus standard care in PCa patients undergoing ADT (for a minimum of 1 year). Subjects in the lifestyle and educational support programs were required to attend 20 small, 90-min group meetings for 6 months. Specifically, subjects in the Lifestyle Program \( (n = 46) \) were taught cognitive-behavioral strategies founded on the transtheoretical model [73, 74] and social cognitive theory [75, 76] to increase PA adherence to 30 min at a moderate intensity on most days of the week. Although no PA instruction was provided, patients were occasionally engaged in 5-min periods of walking, an information session regarding injury prevention and stretching, and a facilitated discussion on a variety of PCa-related topics. Participants in the educational support program \( (n = 51) \) discussed PCa-specific issues, including diet, treatment side effects, and sexuality. Seventy percent and 82% of the participants attended at least half of the lifestyle and educational sessions, respectively. No significant differences were found for health-related QoL, body composition, endurance, 7-day PA volume, caloric expenditure, or social support in any intervention arms. The authors suggest that the lack of efficacy demonstrated with these interventions may be a result of the relatively healthy status (e.g., low levels of anxiety, depression, and pain) of patients at baseline (i.e., a ceiling effect of the intervention). Furthermore, the authors note that their sample size was insufficiently powered due to the onerous and costly nature of conducting a three-armed RCT with strict eligibility criteria (over 1,100 patients were approached). Although the intervention was relatively well received with similar adherence to previous trials, the authors recommend formal PA skills training in conjunction with cognitive-behavioral training to improve the benefits of and adherence to a PA intervention. The results also raise the possibility that professional supervision may be an important component of PA interventions in this group of patients, although this has not been directly tested in an RCT.

Culos-Reed et al. [77] examined the effects of 12-week home-based PA intervention on 31 PCa patients treated with ADT in a pre–post-test research design. A group-based introductory session familiarized subjects with various exercises, consisting primarily of walking, stretching, and light resistance activities.
Resistance bands and exercise balls were provided to subjects to support adherence to this home-based program, with instructions to engage in PA three to five times per week. Group-based “Booster Sessions” that incorporated exercise and discussion were held every 2 weeks to encourage social support, adherence to the program, and measurement of compliance with the program parameters. Results showed that 81% of participants attended at least five of the six booster sessions, with significant post-test differences in volumes of strenuous and total PA, functional capacity, resting heart rate, BMI, and fatigue. A sub-sample \((n = 18)\) was followed for 4 months post-intervention and revealed significant decreases in strenuous PA participation and global health-related QoL. The authors suggest that the reductions in health-related QoL post-intervention may have resulted from a failure to maintain intervention levels of PA, which echoes previous findings from Courneya and Friedenreich [78] in patients with colorectal cancer. Nevertheless, the study by Culos-Reed et al. demonstrates that patients are able to engage in and adhere to home-based exercise programming with similar functional and fitness-related benefits as those achieved in supervised, center-based programs. However, a small sample and lack of randomization and a control group were significant limitations.

Recently, Culos-Reed et al. [79] followed up their initial investigation with an RCT of a home-based exercise program for 100 patients scheduled to receive ADT for at least 6 months. The 16-week exercise program was similar to their previous intervention [77] and included booster sessions. Compared to control subjects, results indicated that intervention subjects had significantly improved PA participation, and waist and neck girth. No significant differences were observed for health-related QoL, depression, or fatigue. Participants attended 78% of the weekly booster sessions, suggesting good tolerance and adherence. Interpretation of these results requires consideration of the lack of statistical power owing to a modest sample size and high dropout rate (34% dropout by 16 weeks). The results of the two studies by Culos-Reed et al. suggest that home-based PA interventions are promising, but limitations necessitate confirmation of the findings in larger, more robust RCTs. The investigators are currently monitoring long-term adherence and benefits in a sub-group of study participants.

Given the substantial physical and functional deterioration associated with ADT, it is not surprising that the majority of research on the effects of exercise has focused on this population of PCa patients. The predominantly chronic duration of hormone ablation makes this treatment population ideal for acute and long-term exercise interventions, as it allows for direct evaluation of the effects on a variety of physical, functional, and psychological outcomes throughout the treatment course.

### 7.3.3 Exercise for Hormone-Refractory Metastatic Disease

No studies have investigated the effect of exercise during chemotherapy for hormone-refractory metastatic PCa. These patients represent a population with
significant challenges to exercise intervention implementation due to limited life-expectancy at this stage of disease (1–3 years). Active trials investigating the effects of chemotherapy are aiming to improve the current life expectancy and exercise interventions targeted at this stage of treatment will be an important area for future research. However, these patients have significant health-related QoL issues secondary to both disease and treatment (e.g., bone pain, fatigue, weight loss), arguing for the design and evaluation of specialized exercise interventions. Only a few studies on the post-treatment effects of exercise have been conducted with samples of mixed solid-tumor survivors that include small sub-samples of PCa patients on chemotherapy [80, 81]. The small sample of PCa patients in these studies does not permit firm conclusions to be drawn.

7.4 Limitations of Current Research

Segal and colleagues’ [51] initial RCT of resistance training for men on ADT is widely regarded as the most methodologically rigorous trial in PCa-exercise research and one of the most rigorous in cancer-related exercise research altogether [82]. Although most exercise studies with PCa patients have used an RCT design [52, 61, 72], small sample sizes, inconsistent use of outcome measures, the absence of intention-to-treat analyses, and a lack of sophisticated measurement of physiological outcomes have presented problems for the interpretation and generalizability of the findings.

The PCa population offers some other unique research challenges. Research in this field has been primarily conducted in northern climates (e.g., Canada) and thus has been susceptible to “snowbird” or “cottage” effects, referring to the characteristic migration of this predominantly retired population to warmer climates during winter months and vacation properties during the summer. This migration may hamper the recruitment, adherence, and efficacy of supervised and/or facility-based exercise interventions. Whether similar challenges exist in PCa patients in other jurisdictions requires formal exploration. Moreover, this population, which often consists of many retirees, may be more likely to consistently engage in exercise interventions which are unsupervised and portable because they have more free time. Adherence findings to home-based interventions in PCa patients have ranged from 64 to 100%. As such, this model should be considered in future trials to address these practical considerations.

Although it appears that exercise interventions are beneficial, well-tolerated, and adhered to during the course of formal intervention for PCa patients, long-term follow-up has not been conducted. The issue of long-term adherence for PCa patients is critical, as the benefits of exercise last only as long as the exercise regimen is maintained [77, 78]. Until long-term adherence is thoroughly investigated, we are left questioning whether exercise interventions are really short-term interventions, beneficial for brief periods (e.g., 12–24 weeks) but ineffective over the longer term. Features that maintain chronic adherence to exercise, such as frequent follow-ups,
booster sessions, home-adaptable exercise regimens, and access to exercise support staff, should be implemented for maximal effect and duration.

### 7.5 Future Directions for Exercise and Prostate Cancer Research

The body of research investigating exercise for PCa patients is growing but additional studies are needed to confirm promising findings in patients treated with EBR or ADT. Furthermore, exercise interventions should be evaluated for PCa patients undergoing other treatments (RP, BT, EM) and in other stages of the disease. In confirming and extending the PCa-exercise literature, various design, sample, measurement, and intervention limitations must be addressed to obtain more precise estimates of exercise benefits. Other researchers have recommended the inclusion of additional clinical outcomes relevant to this population (e.g., osteoporosis, bone fractures, recurrence, progression, and survival) and controlling for various confounding factors (e.g., socioeconomic status, race/ethnicity, medical comorbidity, exercise motivations, past exercise behaviors) [55, 57]. Contamination effects must also be closely monitored as control subjects who adopt new exercise regimens may confound study results, given the impossibility of blinding participants to their assignment of intervention or control group.

It is also necessary to better understand the relevant factors contributing to PA participation. Investigating the determinants of PA and more clearly defining the facilitators/barriers to participation may contribute to the development of more appealing interventions with better adherence rates. Embedding the intervention within a theoretical paradigm possibly offers a more cohesive perspective on the underlying determinants of health-related behavior. Culos-Reed et al. [77, 79] emphasized improved intention-to-exercise by founding their booster sessions on the TPB and demonstrated a high level of adherence despite modest improvements in health-related outcomes. Similarly, Carmack-Taylor et al. [72] founded their lifestyle program on social cognitive theory and the transtheoretical model. In Segal’s first study, application of the transtheoretical model revealed a statistically significant distinction between the contemplation and the preparation stages in predicting exercise adherence [83]. Intention, as defined within the TPB, was also identified as an independent predictor of exercise adherence.

Future studies of exercise in PCa should have a strong emphasis on chronic exercise adherence to facilitate understandings of exercise benefits throughout the course of treatment and beyond. Optimizing long-term adherence will require innovative intervention strategies that are not only acutely beneficial, but are convenient, attractive, and applicable across socioeconomic strata, geographic location, etc. Suggested strategies include the incorporation of social supports, the provision of appropriate exercise equipment and instruction, motivation enhancement tools, satellite exercise facilities proximal to the patient’s home, and home-based, self-directed exercise programs. These are salient factors that should be considered when developing future exercise interventions for PCa patients.
7.6 Exercise Recommendations

The following exercise recommendations for PCa patients reflect the interventions employed in published research trials. Resistance training appears to have a stronger impact on PCa-related side effects than aerobic exercise. However, regular, moderate intensity aerobic exercise should be incorporated into the exercise program to maintain and improve general health, and reduce the risk of comorbidity. Given that the population with PCa has a median age of 68, additional co-morbidities are common and it is strongly recommended that all patients undergo a thorough medical evaluation to determine whether exercise is safe for each patient. Furthermore, an exercise stress test may be useful to define appropriate training intensities and to identify any underlying cardiac conditions.

Aerobic Exercise:
- Frequency: 3–5 times.week\(^{-1}\)
- Intensity: 50–75\% of Max heart rate
- Duration: 30–45 min
- Modality: walking, cycling, elliptical machine

Resistance Training:
- Exercises: compound and single muscle exercises of the upper and lower body; functional exercises resembling activities of daily living
- Equipment: free weights, resistance bands, weight machines, and stability ball
- Volume: 1–2 sets \(\times\) 6–12 repetitions per exercise at 60–70\% of 1 RM; 2–5 times.week\(^{-1}\)
- Progression: increase weight by 5 lb (2.3 kg) after the patient can comfortably lift a weight for 12 repetitions or more

7.7 Summary and Conclusions

In summary, it is evident that exercise plays a beneficial role in maintaining and improving health-related QoL outcomes in men with PCa treated with EBR and ADT. Specifically for patients undergoing EBR, published research indicates that exercise positively impacts fatigue, physical functioning, CV fitness, lower extremity strength, flexibility, body fat percentage, and health-related QoL. For patients undergoing ADT, exercise has also been shown to improve fatigue, physical function, upper and lower body strength, CV fitness, body composition (BMI, waist and neck girth), PA participation levels, and health-related QoL. Future studies are required to clarify the benefit of varying modalities and exercise volumes, as well as the effects of exercise on different treatment groups. Furthermore, an emphasis on long-term exercise adherence is necessary to understand the benefits of exercise beyond the acute intervention phase.
References


Chapter 8
Exercise for Prevention and Treatment of Prostate Cancer: Cellular Mechanisms

R. James Barnard and William J. Aronson

Abstract Numerous epidemiological studies suggest that PA might reduce the risk for PCa but there are many inconsistencies in the data. Little is known about the value of exercise after diagnosis of PCa. Two studies report that resistance training during ADT increases muscular strength and reduces fatigue with no changes in body composition or in serum levels of testosterone or PSA. One study investigated the effects of aerobic exercise training on PCa patients during external beam RT and found an improvement in physical function with reduced fatigue. These were short-term studies with no PCa clinical outcomes. In a 1-year study, regular exercise combined with a low-fat, vegan diet and stress reduction reduced the need for aggressive treatment of the PCa. In obese men with no documented PCa, regular exercise, especially when combined with a low-fat diet, has been shown to reduce serum insulin and IGF-I, while increasing IGFBP-1 and SHBG. These serum changes result in reduced growth and increased apoptosis of androgen-dependent PCa cell lines in cultures. The effects on tumor cells appear to be associated with activation of the p53 gene and suggest that lifestyle modification may be important for both the prevention and treatment of PCa.

8.1 Introduction

The importance of regular exercise for the prevention of common health problems found in the United States and most industrialized nations has been emphasized by most health agencies, including the World Health Organization. Despite this encouragement, the vast majority of individuals do not participate in regular vigorous activity. With regard to PCa, numerous epidemiological studies have investigated the role of PA for prevention with mixed results. In a review published by Thune...
and Furberg [1] it was concluded from the 28 studies that PA, either occupational or leisure, may potentially reduce the risk of PCa by 10–70%. In another review, Lee [2] concluded from 36 studies that the data were inconsistent as to the value of exercise for the prevention of PCa.

With regard to the value of exercise for the treatment of PCa, far less information is available with very few studies being conducted. Three studies investigated the effects of exercise on men during active treatment for PCa. ADT has been traditionally used to treat the later stages of PCa; however, more recently it is regularly used as adjuvant to RT and as therapy for non-metastatic PCa following failure of primary therapy. Although ADT is efficacious in treating PCa there are numerous adverse side effects, including reduced muscle and bone mass with increased fat mass, as well as increased risk of diabetes mellitus and coronary events. Two studies investigated the effects of resistance training during ADT. In a randomized control study, Segal et al. [3] investigated the effects of a 12-week program of resistance training (3× weekly). The training group showed improvement in Fatigue Scale scores as well as in upper- and lower-body muscular fitness. There were no differences between groups for changes in body weight, waist circumference, or skin-fold measurements. Also, there were no differences in serum testosterone or PSA. In a 20-week non-randomized control trial of men undergoing ADT, Galvao et al. [4] found that resistance training produced results similar to the results reported by Segal et al. [3]. Winsor et al. [5] conducted a 4-week trial of walking for 30 min (at least 3× weekly) in men receiving external beam RT. Men in the control group experienced a slight deterioration in physical functioning with increased fatigue while the walking group experienced a significant improvement in physical functioning with no significant increase in fatigue. As these were short-term studies, no clinical outcomes relative to PCa were obtained.

In the Health Professionals’ Follow-up Study of 8 years with 47,524 participants, Giovannucci et al. [6, 7] concluded that vigorous PA not only reduced the risk for the development of PCa, it also slowed the progression and reduced death from PCa. These results suggest an improvement in clinical outcomes. Three large prospective studies [8–10] all reported that PA had a strong effect on decreasing cancer mortality, but did not give data for the various types of cancers. The study by Orsini et al. [10] also reported that the 5-year survival after cancer diagnosis was significantly improved in men who walked or biked for at least 30 min.day⁻¹.

To our knowledge the only study that has investigated the impact of exercise on clinical outcomes in men with PCa was conducted by Ornish et al. [10]. A total of 93 volunteers with PSA 4–10 ng mL⁻¹ and Gleason scores less than seven were randomly assigned to a control group (usual medical care) or an intensive lifestyle intervention group (low-fat, vegan diet, walking 30 min 6× weekly, stress management). Soon after randomization, a few patients dropped out of the study leaving 43 in the control group and 41 in the experimental group. After 1 year, PSA levels had increased in the control group but had decreased in the intervention group, although both changes were small. Six patients in the control group underwent conventional treatment, including RP in three, ADT, EBR, or BT in one each, as recommended
by their personal physicians due to rising PSA or progression of PCa as demonstrated by MRI. In contrast, none of the men in the intervention group underwent conventional treatment.

8.2 Possible Mechanisms for the Value of Exercise

8.2.1 Tumor Growth and Apoptosis

Given that tumor cells need a blood supply to survive and grow, we postulated that changing serum factors might impact on the growth of cancer cells. Thus, we developed a bioassay to study the impact of serum factors on the growth of PCa cell lines in culture. We obtained cell lines from the American Type Culture Collection in Manassas, Virginia, USA, or from other laboratories that had developed specialized lines of interest and grew them in 75-cm² flasks until we had enough cells to do the specific assays of interest. For simple growth assays we used 96-well culture plates and initially plated 5 × 10³ cells.well⁻¹ in medium containing FBS and other factors, as described in detail by Ngo et al. [11]. The following day, after the cells had attached, we removed the medium and replaced it with fresh medium containing 10% FBS (as a control) or 10% human serum from different groups or from the same individual before and after intervention. The cells were grown for 2 or 4 days. Using this same approach we also studied apoptosis by plating 10 × 10³ cells.well⁻¹. Cell growth is determined by CellTiter 96 AQ assay from Promega and apoptosis by the Cell Death Detection ELISA Plus from Roche Applied Science. Initially we used fluorescent stains to detect apoptosis and then determined the percent of apoptotic cells by Adobe Photoshop but found this method to be too time consuming and thus switched to the Cell Death Detection ELISA.

In our initial studies of normal men in their sixties we demonstrated that just 11 days of a low-fat, high-fiber diet and daily exercise altered serum factors that significantly reduced the growth and increased apoptosis of androgen-dependent LNCaP PCa cells [11, 12]. These men were attending the Pritikin Longevity Center Residential Program, so we knew exactly what they were eating and that they were exercising for at least 60 min.day⁻¹. Some of the serum factors that were reduced in men in response to the diet and exercise intervention included insulin and estradiol. Total testosterone was unchanged but sex hormone-binding globulin was increased, indicating a reduction in free testosterone [12, 13]. In separate studies we demonstrated that insulin, estradiol, and testosterone could all independently stimulate the growth of LNCaP cells in culture. When we added all three, insulin, estradiol, and testosterone, back to the post-intervention serum we could only account for half of the reduction in LNCaP growth seen in the post-intervention serum [14].

Next we turned to the IGF axis as IGF-I had been reported to be a risk factor for PCa [15–18]. We found serum IGF-I to be reduced, while IGFBP-1 was increased in response to the diet and exercise intervention [11]. In separate experiments
we showed that adding IGF-I to LNCaP cultures stimulated growth and adding IGFBP-1 reduced growth of LNCaP cells [19]. When we added IGF-I back to the post-intervention serum we completely eliminated the decrease in growth and the increase in apoptosis seen with the intervention, indicating that these serum changes were major factors in the response of androgen-dependent LNCaP cells [19] (Soliman, Aronson and Barnard in press). In addition to the responses of men before and after the 11-day intervention we studied a group of men who had been long-term followers of the low-fat, high-fiber diet and regular exercise lifestyle and found even greater reductions in LNCaP growth and greater increases in apoptosis. In addition to the response to diet and exercise it is important to note that in the pre-samples from obese men, there was robust growth and negligible apoptosis in the serum-stimulated LNCaP cells.

In the later stages of PCa, especially following ADT, the tumor cells often become androgen independent and often develop p53 gene defects [20]. In our initial studies with androgen-independent PC-3 cells we found no significant effect of the diet and exercise intervention on cell growth [12]. In more recent experiments we found a slight decrease in PC-3 cell growth with the intervention but no increase in apoptosis or in p53 protein content (Soliman, Aronson, and Barnard in press). The results with androgen-dependent LNCaP and androgen-independent PC-3 cells suggest that an intensive diet and exercise intervention has the potential to decrease the mitogenicity of serum in men with PCa and favorably impact upon PCa progression, especially in early stages where all PCa is thought to be androgen dependent [20].

In an attempt to separate out the impact of the low-fat, high-fiber diet vs. the impact of daily exercise on the growth and apoptosis of LNCaP cells found with serum from the Pritikin subjects, we contacted Dr. Lawrence Golding at the University of Nevada, Las Vegas. Dr. Golding supervises an adult fitness program where men from the community go to the university 5 days.week−1 for an hour of intensive exercise including calisthenics and swimming, but no dietary intervention. Dr. Golding provided serum samples from 12 men who had participated in the program for a mean of 14.7 years with an average attendance of over 4 days.week−1. Data from these men were compared with data obtained from the eight men of similar age who were long-term followers of the Pritikin diet and exercise lifestyle as well as data from 14 men who were obese controls with no special diet or exercise program [21]. Table 8.1 shows the characteristics of the men in the three groups. There were no significant differences in age among the three groups nor was there any difference in years of lifestyle modification between the Exercise and Diet and Exercise groups. However, there were significant differences in IGF axis factors. Both insulin and IGF-I were lower in the Exercise and in the Diet and Exercise groups compared to controls. IGFBP-1 was significantly higher in both the Exercise and in the Diet and Exercise groups compared to controls and in fact IGFBP-1 was significantly higher in the Diet and Exercise group compared to the Exercise alone group. We hypothesized that these changes in the IGF axis should affect growth and apoptosis of tumor cells.

Figure 8.1 shows the results from serum stimulation of the LNCaP cells from the three groups. The Exercise as well as the Diet and Exercise groups had significantly
reduced LNCaP growth compared to the group of obese control men not undergoing diet or exercise modification. Apoptosis was significantly elevated in both of the intervention groups compared to controls and was significantly higher in the Diet and Exercise group compared to the Exercise only group. In this particular study we used fluorescence staining to detect apoptotic cells. Again we found robust growth and almost no apoptosis in the LNCaP cells stimulated with serum from the control men. We then added IGF-I to both the Exercise and the Diet and Exercise serum and eliminated the reduction in LNCaP growth. In a subsequent study we used the same serum samples in conjunction with tryphostin, an IGF-I/insulin receptor tyrosine kinase inhibitor [22]. Blocking the receptor kinase activity in the control group reduced serum-stimulated LNCaP growth to the same level as was observed in the Exercise group. When the kinase inhibitor was added to the Exercise serum no further reduction in LNCaP growth was noted. Similar results were recently found when we used the IGF-I receptor blocker αIR3 (Soliman, Aronson and Barnard in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control, n = 14</th>
<th>Diet/Exercise, n = 8</th>
<th>Exercise, n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 3</td>
<td>55 ± 4</td>
<td>62 ± 2</td>
</tr>
<tr>
<td>Years in program</td>
<td>–</td>
<td>14.2</td>
<td>14.7</td>
</tr>
<tr>
<td>BMI (kg.m⁻²)</td>
<td>38 ± 2</td>
<td>21.5 ± 3.3</td>
<td>26.5 ± 1</td>
</tr>
<tr>
<td>Insulin (pmol.L⁻¹)</td>
<td>102 ± 27</td>
<td>32 ± 3</td>
<td>41 ± 6</td>
</tr>
<tr>
<td>IGF-I (ng.mL⁻¹)</td>
<td>315 ± 31</td>
<td>143 ± 13</td>
<td>128 ± 12</td>
</tr>
<tr>
<td>IGFBP-1 (ng.mL⁻¹)</td>
<td>22 ± 4</td>
<td>69 ± 12</td>
<td>42 ± 8</td>
</tr>
</tbody>
</table>

All Diet/Exercise as well as Exercise values were significantly different from Control except for age. Diet/Exercise IGFBP-1 was significantly higher than Exercise IGFBP-1. Data are from Barnard et al [21].

![Fig. 8.1](image-url)  
**Fig. 8.1** Effect of diet and/or exercise on growth and apoptosis of serum-stimulated LNCaP cells. Data from Barnard et al. [21]
press, eCAM). To validate the reduction in LNCaP growth with exercise Leung et al. [23] measured the level of PCNA, a marker for cell cycling. PCNA was reduced by 33% in the Exercise group samples, very similar to the reduction in LNCaP growth of 27% observed with the CellTiter assay.

The results collectively indicate that alterations in the IGF axis with diet and/or exercise are the factors primarily responsible for the reduction in LNCaP growth and increase in apoptosis. In a more recent experiment with serum from African-American men, Bond et al. [24] found similar results with LNCaP cells. The men were divided into low or high fitness levels based on maximum oxygen uptake studies. Analysis of serum from the men showed no difference in total testosterone while IGF-I was significantly lower in the high-fitness group. When the serum was used to stimulate LNCaP cells, growth was significantly reduced in the high-fitness group.

How exactly do the alterations in serum IGF factors affect the growth and apoptosis of LNCaP cells? In order to answer this question we relied on the very exciting work related to function of the p53 gene conducted in the laboratory of Dr. Derek Le Roith, primarily by Lisa Heron-Milhavet et al. [25, 26]. The p53 gene is known as the guardian of the genome and is activated upon damage to DNA to protect cells [27]. Initial activation of p53 leads to cell cycle arrest by activating other genes such as p21, p27, and GADD45, followed by activation of DNA repair genes. If the repair fails, apoptosis pathways are activated in an attempt to destroy the damaged cells. Heron-Milhavet et al. [25, 26] showed in cell culture experiments that when DNA was damaged with a UV-mimetic drug, the p53 gene was activated and p53 protein increased, resulting in reduced cellular proliferation and DNA repair. However, when IGF-I was added to the cultures it prevented the cells from undergoing cell cycle arrest/repair by transporting p53 out of the nucleus for degradation. This effect of IGF-I was through the p38 MAPK pathway. Based on these reports we postulated that the serum changes observed in the IGF axis with diet and/or exercise intervention play an important role in the reduced growth and increased apoptosis in serum-stimulated LNCaP cells by increasing the p53 protein content of the cells. This is exactly what Leung et al. [23] and Barnard et al. [22] found. After 2 days of LNCaP growth the p53 protein content of the serum-stimulated LNCaP cells was increased by 100% from $38.2 \pm 2 \text{ pg.g}^{-1}$ protein in the Controls to $75.2 \pm 2 \text{ pg.g}^{-1}$ protein in the Exercise group and was still significantly elevated after 4 days of LNCaP growth in the Exercise group. To further prove that the increase in p53 protein was an important factor in the response observed in the exercise serum-stimulated LNCaP cells, Leung et al. [23] employed a cell line (LN-56) in which a dominant negative fragment of p53 had been inserted into LNCaP cells to block the p53 gene action. With this cell line, growth was not significantly reduced with the exercise serum and apoptosis was reduced as opposed to the significant increase observed in the exercise serum-stimulated LNCaP cells. These results clearly indicate that the impact of exercise training on serum IGF factors directly results in an increase in p53 protein content of the LNCaP cells leading to reduced growth and increased apoptosis.

To further investigate the role of p53 in the response to exercise serum stimulation of LNCaP cells, p21 protein content of the cell lysates was measured and
found to be significantly elevated at 2 days but was back to control at 4 days [22].
This response was at first puzzling as the p53 protein content was still elevated at 4
days and expression of the p21 gene is tightly controlled by p53 protein. However,
Lehman et al. [28] reported similar observations for lung carcinoma cells expressing
wild-type p53. According to Zhang et al. [29] activation of the caspase 3 apoptosis
pathway mediates inactivation of p21 and converts tumor cells from growth arrest
to undergoing apoptosis. This may account for the decrease in p21 protein observed
at 4 days, as we also observed a significant further increase in apoptosis at 4 days.

The significant increase in apoptosis observed in the exercise serum-stimulated
cells is likely due to activation of the mitochondrial apoptotic pathway by p53.
Activation of p53 allows Bax and Bad to insert into the mitochondrial membrane
releasing cytochrome C and other factors that activate the caspase system, result-
ing in apoptosis. Anti-apoptotic proteins such as Bcl-2 and Bcl-xI are increased by
IGF-I and block the insertion of Bax and Bad into the mitochondrial membrane
preventing apoptosis [30]. Thus, we measured Bcl-2 protein in the LNCaP lysates
and found that it was significantly reduced in the exercise serum-stimulated cells
[22]. Another mechanism by which IGF-I might increase tumor growth and inhibit
apoptosis is through inflammatory pathways [31, 32]. We recently measured NFKB
activation in LNCaP cells stimulated with serum following a diet and exercise inter-
vention and found it to be significantly reduced (Soliman, Aronson and Barnard in
press, eCAM).

All of the experiments described thus far were conducted with serum from men
without PCa undergoing diet and/or exercise programs. We were interested to see
if serum from men with PCa undergoing lifestyle modification would have the
same effects on tumor cells. It is well known that PCa tumors and adjacent strom-
al tissues produce IGF-I that may also enter the circulation as well as provide
apocrine/paracrine effects on the tumor cells. We contacted Dr. Ornish when we
heard that he was conducting a randomized trial to treat PCa patients with lifestyle
change and were able to obtain serum samples to use in our bioassay. Figure 8.2
shows the results of the growth and apoptosis experiments with LNCaP cells. Over
the year of observation, growth of LNCaP cells in the bioassay was reduced by
9% in the controls, probably because of some lifestyle changes, while growth was
reduced by 70% in the experimental group [33]. Apoptosis increased in both the
control and experimental groups over the year; however, the increases were not sta-
tistically significant from each other. In addition the increase in apoptosis in the
experimental group, a little over two-fold, was much less than the increase in apop-
tosis found in normal men with diet and exercise intervention that was over 10-fold.
In order to investigate possible reasons for the small increase in apoptosis, espe-
cially in the experimental group, we measured serum IGF factors and found some
interesting results [34]. IGF-I was unchanged in the control group over the year
(153 vs. 170 ng.mL⁻¹) while it increased significantly in the experimental group
(168 vs. 199 ng.mL⁻¹). IGFBP-1 was unchanged in the control group (26 vs.
25 ng mL⁻¹) while increasing significantly in the experimental group (30 vs.
40 ng mL⁻¹). The exact reason for the increase in serum IGF-I in the experimen-
tal group is likely due to the soy supplements (58 g of soy protein power) taken
daily. Several studies, as reviewed in the paper [34], have shown that increased protein consumption results in increased serum IGF-I. It should also be noted that the initial serum IGF-I values were very low as were the initial serum insulin levels (<8 μIU.mL⁻¹). The reason for the very low levels of IGF-I and insulin is unknown but may have been the result of lifestyle changes made by the patients after the initial diagnosis before entering into the study.

In a more recent study Ornish et al. [35] analyzed biopsies of normal prostate tissue obtained before and 3 months after the Ornish lifestyle intervention in a group of 30 patients with very early PCa. The results of gene chip analyses on normal prostate tissue indicated that the intervention resulted in up-regulation of 48 genes and down-regulation of 453 genes. Of the genes down-regulated of particular note were a set of the RSA family of oncogenes and several IGF pathway genes most notably the IGF-IR gene. These results indicate that lifestyle changes can impact on genes related to PCa cancer. It is obvious that more research is needed to fully understand the impact of diet and/or exercise interventions on the clinical outcomes of patients with PCa; however, these small studies by Ornish et al. [33, 35] provide encouragement.

### 8.2.2 Angiogenesis, Invasion, and Metastasis

As indicated earlier, for tumors to survive and grow they require a nutrient and oxygen supply. The nutrient and oxygen supply is provided by new blood and lymph vessels formed by the process of neovascularization. These new vessels also provide avenues for the process of metastasis. The major stimulus for neovascularization is hypoxia which induces the expression of HIF-1α which is involved in the transcriptional regulation of genes such as vascular endothelial growth factor, a major angiogenic gene [38]. In cultured cells IGF-I and IGF-II have been shown to induce
the expression of HIF-1α via the MAPK and PI-3 K pathways. Insulin, known to be reduced by exercise, also activates these pathways indicating that it might be involved in neovascularization [36, 37]. As we have shown that diet and/or regular exercise reduces both insulin and IGF-I, this might play a role in reducing tumor neovascularization in PCa patients.

Once tumors develop and undergo neovascularization they then become invasive through activation of MMPs such as MMP-2 and MMP-9. These proteases degrade the extracellular matrix leading to invasion by the tumors, a process that is optimized by IGF-I [38]. MMPs also increase IGF-I bioavailability by degrading IGFBP-3. This regulatory loop has been reported for the DU-145 PCa cell line [39]. Not only does a low-fat diet and regular exercise lower serum IGF-I, but we also found that they lower MMP-9 [40].

The ability of tumor cells to colonize secondary sites is determined by a combination of both tumor- and host-dependent factors. Brodt et al. [41] identified IGF-I as a major factor promoting metastasis of the Lewis lung carcinoma to the liver. Wu et al. [42] reported that circulating IGF-I played a major role in metastasis of murine colon 38 adenocarcinoma to the liver. The preferred site of metastasis for PCa is bone with significant cross talk between bone and tumor cells [43]. IGF-I and IGF-II are the most abundant proteins in bone and are important for normal growth and development. However, factors secreted from the tumor cells lead to bone demineralization and fractures while the bone IGF’s might induce tumor proliferation and invasion while blocking apoptosis. According to Kingsley et al. [43] specific contributions of the IGF’s to bone metastasis are surprisingly untested. However, in biopsies from PCa patients with bone metastasis the IGF-IR was frequently increased [44]. Collectively these data suggest that IGF factors might play an important role in PCa metastasis and that regular exercise may have the potential to delay metastasis by altering the IGF axis factors as discussed earlier. This suggestion is supported by data from the Health Professionals’ Follow-up Study reporting that vigorous exercise slowed progression and reduced PCa death [7].

8.3 Summary and Conclusions

In spite of lack of clinical trials demonstrating the efficacy of a exercise for the prevention and treatment of PCa, the experimental data from cell culture studies indicate that it should be important. As presented above, regular exercise in older men alters serum factors that reduce growth and increase apoptosis in the androgen-dependent LNCaP cell line and reduce growth of androgen-independent PC-3 cells. The alterations in serum resulting from regular exercise include reduced insulin and IGF-I with increased IGFBP-1 and SHBG. Of these changes, the reduction in IGF-I appears to be the most important factor. Reducing IGF-I results in increased levels of the p53 and p21 proteins, with reductions in Bcl-2 protein, as well as reduced NF-kB activation in LNCaP cells. Based on these data, randomized prospective trials, aimed at evaluating the effects of exercise on clinical outcomes and relevant serum and tissue biomarkers in men with PCa, are indicated. As IGF-I may provide ‘escape
mechanisms’ from radio and/or chemotherapy, leading to more aggressive phenotypes [38], exercise may be potentially useful as an adjuvant to these established cancer therapies.

Surprisingly, little attention has been paid to the effect of exercise on serum IGF-II even though its concentration is three to five times greater than that of IGF-I. Although the IGF-II receptor has no intercellular signaling mechanism and is thought to be primarily a docking protein limiting IGF-II bioavailability, IGF-II can bind to and activate both IGF-IR and IR-A that might play some role in growth and apoptosis as well as metastasis of cancer cells [45].

Acknowledgments This work was supported by NCI Specialized Program of Research Excellence Grant P50 CA-921310, NCI Grant R01 CA-100938, The Veterans Administration, and a donation from the L.B. Research and Education Foundation.

References

Chapter 9
Physical Activity Before and After Diagnosis of Colorectal Cancer

David J. Harriss, N. Tim Cable, Keith George, Thomas Reilly, Andrew G. Renehan, and Najib Haboubi

Abstract Physical inactivity is responsible for 13–14% of colon cancer, an attributable risk greater than family history. Epidemiological evidence shows that PA is protective against colon cancer but is inconclusive as to whether it is protective of rectal cancer or has equal effects on male and female risk of colorectal cancer. The effect of exercise interventions on the risk of colorectal cancer is currently not known; however, the results of a recently published 12-month training programme are encouraging. Although inferences can be made from epidemiological studies, no optimal exercise regimen can be confidently prescribed for protection against colorectal cancer. The limited available evidence demonstrates potential benefits of being physically active before diagnosis of colorectal cancer for disease-specific survival and prognosis. Studies undertaken on survivors of colorectal cancer provide the basis for future research which should be designed to more directly investigate the effect of exercise interventions on clinical outcome measures. Markers/mechanisms by which the impact of PA may be measured include GTT, chronic inflammation, immune function, insulin levels, IGF, genetics and obesity. Research studies have been proposed to help assess whether these markers are beneficially affected by PA, either before or after diagnosis of colorectal cancer. This chapter reviews our current understanding of the significant impact of PA on the risk of, and survival from, colorectal cancer and provides directions for future research which will underpin future health care policies and practices.

9.1 Introduction

An estimated 639,000 people die worldwide each year of colorectal cancer and incidence rates have been estimated at 1 million per annum, constituting 9% of new cancer cases [1]. There is a 25-fold variation in the incidence of colorectal cancer

D.J. Harriss (✉)
Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK
e-mail: d.harriss@ljmu.ac.uk
worldwide, with the highest incidence occurring in the more economically developed regions such as North America and Western Europe and lower incidence in less developed regions such as Africa and Asia (see Fig. 9.1). It is reasonable to conclude that the geographical differences are due to exposure to a ‘westernised’ environment since Asian migrants to the USA acquire risks similar to the local population [2].

Altogether 70–80% of colorectal cancer cases may be attributable to environmental causes [3]. Physical inactivity appears responsible for between 13 and 14% of colon cancer cases, with poor diet responsible for 12% [4]. The risk from physical inactivity is greater than the risk due to family history but these factors may be additive. In individuals with a family history of the disease, Slattery et al. [5] observed a lower risk of colorectal cancer in those reporting the highest physical activity levels ($RR = 2.09$ (95% CI, 1.44–3.04)) compared to those with the lowest reported PA levels ($RR = 2.64$ (95% CI, 1.78–3.92)). As PA programmes can lead to reductions in body weight and body fat and is associated with a healthier diet, non-smoking and low alcohol consumption, the link between physical inactivity and colorectal cancer is not surprising.

In the next section of this chapter, an overview of epidemiological evidence is presented to demonstrate that PA is associated with a reduced risk of colorectal cancer. The limited research in relation to (a) PA before and after a diagnosis of colorectal cancer in relation to recurrence and survival from the disease and (b) the effect of PA on response pathways and biomarkers of colorectal cancer before diagnosis and in survivors of colorectal cancer is then considered in the following two sections. Particular attention is given to investigations in which epidemiological and experimental research designs were employed to study the impact of PA on risk and recurrence of colorectal cancer and possible response pathways and biomarkers.
of colorectal cancer. The evidence linking PA and colorectal cancer, both before diagnosis and after treatment, is weighed up in the concluding section.

9.2 Physical Activity and the Risk of Colorectal Cancer

There is epidemiological evidence of an association between physical inactivity and colorectal cancer risk. A caveat is that many of the measures of PA are weak, and few studies refer to life-long PA. There is also a need to distinguish between formal exercise regimens and free-living PA, a distinction not made in many studies. Compelling evidence from intervention studies is still awaited.

A meta-analysis conducted by the C-CLEAR group [6] of 14 cohort studies showed a modest 20% and 14% reduced risk of colon cancer in males and females, respectively, when comparing those most active to least active in their leisure time. With regard to rectal cancer, analysis of eight cohort studies failed to show that leisure-time PA provides any significant protective effect. Some authors have reported a protective effect of PA for distal tumours whilst others showed associations for proximal tumours. Research groups that measured the effects of PA on both the distal and proximal colon have generally reported the effect of PA to be more pronounced in the distal colon [4].

Invasive cancer is usually preceded by colorectal adenomas, which can indicate risk of colorectal cancer, although only 1–10% of people with adenoma will later develop colorectal cancer [7]. Fourteen out of 19 published case–control and cohort studies on PA and adenomatous polyps have indicated statistically significant inverse relationships with PA, and 5 have found no relationship [8–10]. A stronger negative association between PA and advanced adenomas compared to low-risk adenomas has been observed in some but not all studies. A cross-sectional comparison of lifestyle effects on adenoma between participants with no neoplasia, low-risk adenomas and advanced neoplasia showed that the patients with advanced adenomas were twice as likely not to adhere to lifestyle recommendations. However, there was no significant association with PA [11].

Whilst there is strong evidence of a protective role based on association between PA and colorectal cancer, intervention studies are needed to show more directly whether PA causes a reduced risk of the disease. In the only published intervention study related to risk of colorectal cancer in humans, a 12-month moderate-to-vigorous intensity aerobic exercise intervention resulted in no change in colon mucosal prostaglandin concentrations [12], but there were significant decreases in colon crypt cell proliferation indices in men who exercised more vigorously (a mean of >250 min.week⁻¹) or whose maximal oxygen consumption increased by >5% [13]. The benefit of more vigorous PA observed in this study is consistent with epidemiological evidence which shows a greater reduction in risk of colorectal cancer with greater amounts of PA [6]. However, it is not yet known whether vigorous or higher volumes of are required to reduce the risk of colorectal cancer.

Comparisons between intervention studies animals and of humans are limited by the difficulties in comparing amounts of PA and the differences in tumour
development. However, intervention studies of animals provide some support to accompany the epidemiological evidence. Basterfield et al. [14] reviewed eight studies that used rodent models. Five studies using carcinogen-treated rats showed that tumour incidence was reduced by 32–52% with PA. However, three studies using mice that developed multiple intestinal polyps spontaneously yielded no evidence that PA reduced intestinal neoplasia. The difference in results could have been due to reduced ‘non-structured exercise’ PA in these studies, in which the mice maintained their energy balance, rather than experience a negative energy balance. However, an alternative explanation could be that PA does not affect the risk of adenoma in the small bowel, which is the predominant form of adenoma in mice.

9.2.1 Dose–Response

The dimensions of PA are its frequency, duration and relative/absolute intensity. Whether a reduction in colorectal cancer risk is determined by an increase in one or more of these factors and whether the factors operate independently of each other are unknown. Figure 9.2 shows the results of a dose–response meta-analysis of 14 cohort studies [6]. The diversity of PA indices used and the differences in the number of PA categories preclude direct conversion to a common scale of energy expenditure. Therefore, risk ratios were estimated as a function of cumulative percentiles for the distribution of leisure-time PA in a study population. In this method, a continuum of sample centiles is conceptualised for each study, ranging from the least active referent centile (assigned an RR of 1) to the highest percentile of participants in the population who are most physically active. The results were consistent with linear patterns of reduction in colon cancer risk for both genders. As the ‘early’ percentiles are mostly referent categories, risk was unity up to the 20th percentile of leisure-time PA, after which there was a linear reduction in risk across the 20th to 95th percentiles. The effect was attributed to either, or a combination of, an increase in frequency, duration or relative/absolute intensity of PA.

The epidemiological evidence suggests that high-intensity PA may stimulate the biological mechanisms that protect against colorectal cancer. However, there are contrary effects as high-intensity PA can increase the production of oxygen free radicals, enhance the depletion of antioxidant defences [15] and depress immune function [16] and so a note of caution is advised. Oxygen free radicals can damage lipids, protein and DNA. Such alterations can cause cell mutagenesis and promote tumour proliferation [17]. Demarzo et al. [18] observed a significantly increased number of aberrant crypt foci, which may develop into colorectal cancer, in the colon of untrained rats treated with a colon carcinogen 15 days after a single bout of exhaustive swimming. Conversely, PA at moderate intensity may be beneficial as the response of the antioxidant system is increased more than the increase in oxygen free radicals [19]. To date, the dose–response issue has not been directly addressed in an experimental intervention to establish an appropriate exercise prescription to reduce the risk of colorectal cancer, avoid recurrence or extend survival time.
9.3 Physical Activity, Recurrence of and Survival from Colorectal Cancer

The effects of PA or physical fitness before diagnosis of colorectal cancer on disease prognosis have been examined in three studies. Haydon et al. [20] conducted a prospective cohort study of 41,528 people by measuring body size and PA levels with questionnaires at baseline and then recorded survival from colorectal cancer (diagnosis was a median of 5.3 years after baseline) in 526 cases during follow-up. Individuals who reported undertaking regular PA had an age-adjusted 12% greater disease-specific survival (see Fig. 9.3) compared to those that were classified as non-exercisers. The survival figure rose to 39% in a sub-group of individuals with stage II or III tumours at diagnosis. Results from the Danish Colorectal Cancer Group patients showed that self-perceived physical fitness at or below the group average
before diagnosis increased the risk of general complications, thrombosis and mortality during the 30-day post-operative period [21]. However, a prospective observation study of 573 women failed to find any association between pre-diagnosis PA and mortality [22].

Most cancer patients reduce their level of PA after diagnosis so the benefit of prior PA may be lost. This decrease in PA may explain increases in body mass, which could have a negative effect on prognosis [23]. The evidence for the benefits of a PA intervention after diagnosis of colorectal cancer is limited. The focus of most studies to date has been the feasibility of performing PA interventions in survivors and the effect of such activity on both physiological and psychological processes [24–26]. Very few studies have been conducted on the effects of PA on survival from, or biological markers of, colorectal cancer.

Studies that have been conducted in the post-diagnosis period report positive outcomes in relation to disease prognosis. Following primary therapy for colorectal cancer, Allgayer et al. [27] exercised 19 patients daily for 30–40 min at moderate (30–40% of maximal capacity) or high-intensity (50–60% of maximal capacity) exercise for 2 weeks. Following the moderate-intensity exercise, but not the high-intensity exercise, urinary excretion of 8-oxo-dG, a product of DNA damage believed to be important for tumour formation, was significantly reduced from 8.47±1.99 to 5.81±1.45 ng.mg⁻¹ creatinine. The longer-term implications of moderate-intensity exercise for tumour spread and cancer relapse are as yet unknown. Nevertheless, these results may help to explain the improvement in disease-free survival reported by Meyerhardt et al. [28] in patients that were physically active in the post-diagnosis period. Meyerhardt et al. [22] prospectively studied recreational PA among 816 patients 6 months after adjuvant chemotherapy (and

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**Fig. 9.3** Kaplan–Meier curves for colorectal cancer survival by exercise group [20]
14 months after surgery for stage III colorectal cancer). Patients reporting 18–26.9 MET-h.week\(^{-1}\) of PA in the previous 2 months had a HR for disease-free survival of 0.51 compared to those that were physically inactive. There was no additional improvement in the HR for disease-free survival for those that reported more than 27 MET-h.week\(^{-1}\) of PA. These studies provide the basis for PA intervention trials in survivors of cancer. Courneya et al. [29] and Spence et al. [30] have published research proposals which aim to determine the effects of PA interventions on outcomes, such as disease-free survival, physical functioning, biomarkers and indices of fatigue and QoL, in survivors of colorectal cancer who have completed adjuvant therapy.

There is encouraging evidence from animal studies for prescribing exercise programmes as an adjunct therapy in cancer treatment to reduce tumour growth and attenuate symptoms of cachexia. de Lima et al. [31] reported a 34% reduction in tumour weight in tumour-bearing rats following 6 weeks of exercise training, along with a significantly lower reduction in body weight compared to controls. Bacurau et al. [32] reported a 10% reduction in tumour mass and a 2.8-fold increase in lifespan of tumour-bearing rats following 10 weeks of treadmill running.

### 9.3.1 Quality of Life Issues

Even though survival from colorectal cancer is improving with progress in diagnosis and treatment, the treatments are still toxic and have negative physiological and psychological consequences such as pain, reduced cardiorespiratory fitness, fatigue, anxiety, depression, reduced self-esteem, reduced QoL and suppressed immune function [33]. Functional QoL has the strongest relationship with overall satisfaction with life [34]. Courneya and Friedenreich [34] reported that breast cancer patients who repeatedly relapsed from exercise reported lowest QoL scores. A systematic review and meta-analysis of exercise interventions indicated that the cardiorespiratory fitness of cancer patients was moderately improved both during and after cancer treatment [35]. Additionally, an exercise intervention during cancer treatment was associated with a small to moderate positive effect for symptoms and side effects of treatment. These results were based on limited research evidence and therefore more studies need to be conducted to assess the clinical impact and to draw conclusions on other measures of QoL. The effects of PA before treatment, palliation of symptoms at the end of life, long-term health promotion and survival after successful eradication of cancer are also areas for future studies [35].

### 9.3.2 Co-morbidities

Risk factors for colorectal cancer such as physical inactivity and obesity are also risk factors for non-cancerous diseases such as CV disease and metabolic syndrome [36]. Even though cancer patients may survive cancer treatment they may
still be at risk from co-morbidities. CV disease (10–30%), hypertension (11–25%), chronic obstructive disease (3–25%) and diabetes (5–25%) are the most frequent co-morbidities in cancer patients [37]. Participants treated for colorectal cancer in Queensland, Australia, between 1982 and 2002 were found to have nearly a 40% higher risk of non-cancer mortality and a 25% higher risk of CV mortality compared to the general population [38]. Whether PA after diagnosis of colorectal cancer can have an impact on the risk of non-cancer mortality compared to those not previously diagnosed with colorectal cancer is unknown.

9.4 Physical Activity, Response Pathways and Biomarkers of Colorectal Cancer

Observational evidence of a protective effect of PA against colorectal cancer implicates several mechanisms, although there is limited empirical support for these as putative explanations. The response pathways and biomarkers of colorectal cancer need to be identified in order to assess the effects of PA in protecting against and improving the clinical outcomes of a colorectal cancer diagnosis.

9.4.1 Gastrointestinal Transit-Time

A decrease in GTT induced by PA could protect against colorectal cancer by decreasing exposure of the colon mucosa to carcinogens in the faecal stream [39], decreasing the concentration of bile acids [40] or by decreasing colonic segmentation. Walking [41, 42], running [43, 44] and strength training [45] have been found to reduce GTT. Conversely, a period of physical inactivity in participants who had engaged in regular PA for 10 years significantly increased GTT [46]. However, some authors have reported no effect of PA on GTT [47–49]. Changes in GTT induced by PA might have limited impact upon colorectal cancer risk, as reducing exposure of colon mucosa to carcinogens by adopting a diet low in fat [50], high in fibre [51] or high in antioxidant micronutrients [50] does not influence the risk of colorectal adenomas. However, the association between the risk of colorectal cancer or disease prognosis and PA-induced reductions in GTT remains to be investigated.

9.4.2 Chronic Inflammation

Chronic inflammation may contribute to the development of approximately 15% of cancers worldwide [52] and may be a critical component of the progression of colorectal cancer [53]. There has been no study in humans of the association between risk of colorectal cancer or disease prognosis and PA-induced reductions in chronic inflammation or the association between PA and chronic inflammation in survivors of colorectal cancer and the consequences for clinical outcomes.
However, exercise interventions have been conducted in rats that have been injected with dimethylhydrazine immediately after each exercise protocol in order to induce increased colonic epithelial cell proliferation and increase the expression of the inflammation-related enzyme cyclooxygenase-2 [54]. Cyclooxygenase-2 expression was significantly attenuated following 8 weeks of swim training suggesting an anti-inflammatory response.

Chronic inflammation may cause mutations of genes controlling growth, DNA repair and programmed cell death, which are prime targets for the oncogenic process of proliferation, survival and migration of cells [55]. Studies on inflammatory bowel disease indicate that patients with long-term ulcerative colitis have up to a 10-fold higher risk of developing colorectal cancer [56]. These results are supported by experimental animal models of colitis [14]. Faecal calprotectin, a marker of bowel inflammation, was reported to be increased in patients with colorectal cancer [57] and higher in patients with adenomas compared to normal participants [58]. The use of NSAIDs has been found to be inversely related to colorectal cancer risk and in randomised control trials to reduce the formation of colorectal adenomatous polyps [56].

The belief that PA favourably modulates colonic inflammation is supported by epidemiological investigations. A significant positive relationship between calprotectin and physical inactivity was reported by Poullis et al. [59]. Hauret et al. [60] also observed that an association between PA and adenoma was not detected among users of NSAIDS but the inverse effect of PA on adenomas was apparent in non-users of NSAIDS with an RR of 0.49 (95% CI, 0.25–0.94). The mechanism by which PA reduces chronic inflammation has not been established but may reflect changes in pro-inflammatory markers, such as prostaglandin E2, TNF-α, CRP and IL-6.

An increase in prostaglandin production in tumours has been associated with colorectal tumour progression, and prostaglandin E2 is elevated in human colorectal cancers and adenomas in familial adenomatous polyposis patients [61]. Participants who reported higher PA levels were found to have a 28% decrease in prostaglandin E2 [62].

High levels of IL-6 are found in colorectal cancer patients, and pharmacological and dietary methods used to decrease IL-6 have yielded promising results in treating colon cancer in animal models [63]. An inverse but complex association between PA and IL-6 is supported by epidemiological evidence [64]. Physically active older men had significantly lower levels of IL-6 compared to inactive men in a study by Jankord and Jemiolo [65]. Resistance training and aerobic exercise over 12 weeks [66], 24 weeks [67] and 6 months [68] duration resulted in a decrease in IL-6 in younger and older men, a decrease in TNF-α and CRP in men and women and a decrease in IL-6 and CRPs in obese post-menopausal women, respectively.

TLR4, a trans-membrane protein, may play a role in regulating the link between inflammatory cytokine production and PA. Stimulation of TLR4 mediates the production of inflammatory cytokines and activation of innate immunity via nuclear factor-kB [69]. Participants who expressed high levels of TLR4 produce significantly more IL-6 and TNF-alpha, and TLR4 mRNA was significantly lower in
resistance-trained compared to untrained older women [70]. In accordance with these findings, McFarlin et al. [71] showed that monocyte surface expression of TLR4 was about 2.5 times lower in resistance-trained compared to untrained postmenopausal women and Stewart et al. [66] reported that a combination of resistance training and aerobic exercise over 12 weeks decreased the expression of TLR4 on lipopolysaccharide receptors.

9.4.3 Immune Function

Tumour cells are normally detected and eliminated by the body’s immunological surveillance mechanisms [72]. Impaired immune function has been considered a ‘hallmark of malignant disorders’ [73] either as a result of initiation, development or treatment of cancer. Patients with colorectal cancer who had higher natural killer cell cytotoxicity before immunotherapy were reported to have a greater overall survival [74]. Suppression of both adaptive and innate immune systems may be a means by which chronic inflammation constitutes a risk factor for colorectal cancer [55]. An association between risk of colorectal cancer or disease prognosis and PA-induced enhancement in immune function has not been studied.

Training regularly at moderate intensity has been found to enhance immunological surveillance processes such as proliferation of lymphocytes, increased natural killer cell activity and increased lymphokine-activated killer cells [75]. The protective benefits of aerobic exercise training against a 24-hours 33–50% immunosuppression following persistent stress such as footshock have been demonstrated in animal models [76, 77]. Exercise training may also help to maintain adequate immune response to stress. However, a meta-analysis of the response of natural killer cell count and cytolytic activity to aerobic exercise training indicated that any benefits were small and statistically non-significant [16].

Cancer treatments, including surgery, chemotherapy and RT, are immunosuppressive. The link between changes in the immune system due to cancer treatment and cancer outcomes has not been established [78]. Some studies of the effect of PA on immune function in survivors of cancer have suggested beneficial results, but others have not. No differences in circulating T-cell or natural killer cell count or activity in response to 8 weeks of resistance training were found in patients who had undergone surgery, chemotherapy and/or radiation treatment for breast cancer [79]. Also, Hayes et al. [80] reported that exercise training at 70–90% HRmax for 3 months did not improve, or more importantly delay, the recovery of immune cells from high-dose chemotherapy.

Allgayer et al. [81] examined the effects of a moderate-intensity exercise rehabilitation programme in patients with colorectal tumours on immune function. Production of IL-1ra and the IL-1ra/IL-6 ratio were decreased following the programme, suggesting a decreased anti-inflammatory and an increased pro-inflammatory response. The impact on clinical outcomes resulting from a decreased susceptibility to infection is unknown.
The relationship between immune function and PA may not be linear. High-intensity PA may be immunosuppressive, as increases in upper respiratory tract infection and decreases in natural killer cell count and activity have been reported following bouts of strenuous exercise [82] as well as DNA damage to peripheral leucocytes [83]. As the participants used in these studies had relatively high cardiopulmonary fitness levels, the strenuous exercise performed was likely to require absolute exercise intensities that are greater than those reported in epidemiological studies or intervention studies of survivors of colorectal cancer. The clinical significance of changes in immune function with PA is not yet known.

### 9.4.4 Insulin

Insulin resistance and hyperinsulinaemia are thought to be linked to colorectal cancer. In separating risks for colon cancer and rectal cancer, Hu et al. [84] observed a greater risk in patients with diabetes for colon cancer (RR = 1.49 (95% CI, 1.09–2.06)) than rectal cancer (RR = 1.11 (95% CI, 0.56–2.21)). These figures were reversed by La Vecchia et al. [85] who reported a risk ratio of 1.2 (95% CI, 0.8–1.6) for colon cancer and 1.5 (95% CI, 1.1–2.2) for rectal cancer. Two case–control studies indicated that participants in the highest quartile of insulin were more likely to have an adenoma [86, 87] and to have the lowest apoptosis [86] compared with the lowest quartile, suggesting that hyperinsulinaemia may be an early risk factor for colorectal cancer. Kaaks et al. [88] found that elevated C-peptide, a biologic marker of hyperinsulinaemia, was associated with an increased risk of colorectal cancer incidence, up to an OR of 2.92 (95% CI, 1.26–6.75) and Ma et al. [89] reported that an elevated C-peptide concentration was associated with a 2.7-fold (95% CI, 1.2–6.2) increased risk of colorectal cancer. Furthermore, insulin and glucose levels were significantly higher in colon cancer patients before surgery than in controls [90].

Results from large-scale clinical trials and exercise intervention studies suggest that PA protects against and decreases insulin resistance, hyperinsulinaemia and glucose intolerance [91]. However, the evidence for a direct causal link between PA, insulin resistance and colorectal cancer has not been established. Platz et al. [92] failed to find any relationship between PA, glycosylated haemoglobin and colorectal cancer or adenoma risk.

The effects of PA on insulin resistance or hyperinsulinaemia in survivors of colorectal cancer have not been studied. In survivors of breast cancer PA has been negatively associated with C-peptide [93]. Resistance training [94] and aerobic type exercise [95] had no effect on insulin levels or insulin resistance. Nevertheless, more research is required to assess whether PA may help in protecting against insulin resistance and therefore reduce the likelihood of cancer recurrence.

#### 9.4.4.1 Insulin-Like Growth Factor

The IGF system has been highlighted as a risk factor for colorectal cancer because of its role in regulating cellular proliferation. It has been consistently found that IGF-II
is over-expressed in cancer cell lines, whereas the evidence for over-expression of IGF-I is not as consistent [96]. There is support from epidemiological studies of a relationship between IGF-I levels and the risk of colorectal cancer, whereas only a few studies have indicated that IGF-II is a possible risk factor [88, 96, 97]. Renehan et al. [98] reported an RR for high-risk adenomas of 4.39 (95% CI, 1.31–14.7) with increased IGF-I levels. Conversely, Keku et al. [86] found no significant differences in circulating IGF-I or IGF-II levels among cases of adenomas and controls. A meta-analysis report by Renehan et al. [99] confirmed that case–control studies might have overestimated the relationship between IGFs and colorectal cancer and therefore highlighted the need for prospective studies.

The association between risk of colorectal cancer and changes in circulating IGFs induced by PA has not been formally examined. Reduction of circulating IGF levels via PA could attenuate the impact of this potential risk factor. Generally, epidemiological studies have failed to show an association between PA and levels of IGFs [97, 100–104]. However, Haydon et al. [105] reported that for the physically active, an increase of IGFBP-3 by 26.2 nmol.L⁻¹ before diagnosis was associated with a 48% (HR = 0.52 (95% CI, 0.33–0.83)) reduction in deaths from colorectal cancer. The complexity of the relationship between PA and IGFs is highlighted by a cross-sectional study and exercise training studies. A significant elevation of IGF-I was reported in middle-aged cycle-trained men compared to an untrained group [106], but a reduction followed 11 weeks of intense endurance-type exercise training in untrained and well-trained individuals [107]. Also, Poehlman et al. [108] reported a 19% increase in men and no change in IGF-I levels in women following 8 weeks of endurance training. Fialaire et al. [109] and Gomez-Merino et al. [110] found a decrease in IGFBP-3 in response to 16 weeks of exercise training for gymnastic competition and 3 weeks of military exercise training, respectively. In contrast, 11 weeks of intense military exercise training increased IGFBP-3 in previously untrained individuals [107]. It is possible that effects vary with the mode of exercise, fitness level of participants and other factors.

The relationship between PA and IGFs may be explained by an interaction between PA and energy balance. Nemet et al. [111] reported a significant reduction in IGF-I in underfed participants undertaking aerobic exercise training, whereas there was no change in the participants who were overfed. The authors suggested that the very fast recovery of IGF-I values to pre-intervention levels could be the reason for some of the inconsistencies between cross-sectional and prospective studies of exercise training and IGF-I. The association between PA and IGFs has not been investigated in survivors of colorectal cancer. However, in breast cancer survivors, PA was associated with higher IGFBP-3 and IGF-I:IGFBP-3 ratio [93].

9.4.5 Genetic Mutations

The belief that PA up-regulates or down-regulates genes involved in the colorectal cancer disease process has little empirical support. However, PA has been negatively associated with \( p53 \) and \( Ki-ras \) gene mutations. The \( p53 \) gene has been closely
associated with the transition from adenoma to carcinoma in colorectal cancer [112], and \( Ki\text{-ras} \) mutations may occur in 30–50% of colon tumours [113–115].

Leung et al. [116] reported that participants who were part of a 1-h.day\(^{-1}\), 5 days.week\(^{-1}\) PA programme for at least 10 years showed reductions in serum IGF-I and increases in IGFBP-1, which increased the function of the \( p53 \) gene in PCa cells. Additionally, a case–control study of 1,428 cases of colorectal cancer and 2,410 controls showed that men, but not women, with low levels of PA were more likely to have a colon cancer tumour with the \( Ki\text{-ras} \) mutation than one without this mutation [117]. PA may affect other genes implicated in colorectal cancer such as the tumour suppressor \( APC \) gene, genes on the long arm of chromosome 18 (\( 18q \)) or the mismatch repair genes [118].

The association between PA and gene mutations has not been investigated in human survivors of colorectal cancer. However, using DNA microarrays researchers were able to compare mRNA expression levels of approximately 10,000 genes in the colon mucosa of rats following voluntary exercise for 12 weeks [119]. A 10-fold repression of the betaine-homocysteine methyltransferase 2 gene in the colon mucosa was reported, a possible mechanism for exercise training protecting against aberrant DNA methylation, a common event in cancer development.

### 9.4.6 Obesity

The BMI and waist-to-hip ratio have been used as surrogates of body adiposity in public health studies. A meta-analysis conducted by the C-CLEAR group [120] reported that for every 5 kg m\(^{-2}\) increase in BMI, RR for colon cancer was 1.24 (95% CI, 1.20–1.28) in men and 1.09 (95% CI, 1.04–1.12) in women and RR for rectal cancer was 1.09 (95% CI, 1.05–1.14) in men. MacInnis et al. [121, 122] reported that high waist-to-hip ratio, an estimation of central adiposity, was significantly associated with colon cancer, with an RR of 2.1 (95% CI, 1.3–3.4) and 1.31 (95% CI, 1.08–1.58) in men and women, respectively. Slattery et al. [123] reported that compared to men and pre-menopausal women with a high level of PA and a BMI of less than 23 kg m\(^{-2}\), the risk of colon cancer for physically inactive individuals with a BMI of greater than 30 kg m\(^{-2}\) was 3.64 (95% CI, 1.96–6.77) and 3.22 (95% CI, 1.47–7.04), respectively. Also, Mao et al. [124] observed that compared to men and women with PA levels greater than 24.6 MET-h.week\(^{-1}\) and with a BMI of less than 25 kg.m\(^{-2}\), the risk of rectal cancer was 1.58 (95% CI, 0.98–2.55) and 1.79 (95% CI, 1.07–2.99), respectively, for physically inactive individuals with a BMI of greater than 30 kg m\(^{-2}\).

PA is a major component of daily energy expenditure, and it can be increased to achieve a negative energy balance, which is an important determinant of weight loss. A moderately strong relationship between physical inactivity and obesity is supported by epidemiological research [125]. A review of randomised controlled trials in small populations indicated that overweight participants who exercised but did not change their diet lost an average of only 2.3 kg more than non-exercisers during
a 9-month period [126]. By strictly controlling energy expenditure and energy intake as a result of recruiting participants into a residential facility, Bouchard et al. [127] reported that males lost an average of 8 kg after a 3-month period. Reductions in body fat may be underestimated by reductions in body mass because any change in body mass could include increases in muscle mass acquired as a result of the activity causing increased energy expenditure. It would be useful if body composition compartments could be measured more precisely by, for example, using DEXA rather than relying on gross and indirect measures such as BMI. Additionally, increases in energy expenditure induced by PA may significantly reduce central adiposity [126]. However, it is not known whether treating obesity by preferentially increasing PA, restricting energy intake or combining the two is optimal for reducing the risk of colorectal cancer [128].

9.5 Summary and Conclusions

Epidemiological evidence shows that PA is associated with a decreased risk of colorectal cancer and may be associated with greater survival following diagnosis. Although a dose–response relationship can be inferred from these epidemiological studies, the optimal exercise prescription is unknown, as intervention studies are lacking. The research evidence is at best limited with respect to whether PA after diagnosis, during treatment and after treatment for colorectal cancer has clinical, physiological or psychological benefits, but what evidence we do have has been encouraging, highlighting the need for further work. The effects of PA on the response pathways and biomarkers of colorectal cancer prior to diagnosis and in the post-diagnosis periods should be investigated with respect to gender, age, obesity status, daily energy intake and exercise prescription.

Acknowledgments This manuscript was supported by a grant from Trafford General Hospital NHS Trust. The authors have no conflicts of interest that are directly relevant to the content of this review.

References


Chapter 10
Exercise-Based Rehabilitation in Patients with Lung Cancer

Martijn A. Spruit, Khaled Mansour, Emiel F.M. Wouters, and Monique M. Hochstenbag

Abstract Lung cancer was a rare disease at the start of the last century, but exposures to new etiologic agents and an increasing lifespan have combined to make it one of the most prevalent forms of the disease in the 21st century. Furthermore, lung cancer remains the most common cause of cancer-related death. Pre-operative QoL and exercise capacity are poor in patients with lung cancer and become worse following (surgical) treatment. Moreover, post-operative recovery of QoL and exercise tolerance are only partial over extended periods of time. Therefore, in patients with lung cancer, there is a clear indication for comprehensive peri- and post-operative exercise-based rehabilitation. Indeed, exercise-based pulmonary rehabilitation could prove to be a powerful non-pharmacological intervention to improve exercise performance and health status, irrespective of change in pulmonary function. To date, the effects of exercise-based rehabilitation in patients with lung cancer have not been extensively studied but preliminary results from small-scale intervention studies suggest that lung cancer patients are good candidates for peri- and post-operative pulmonary rehabilitation programmes.

10.1 Introduction

Lung cancer was a rare disease at the start of the last century, but exposures to new etiologic agents and an increasing lifespan have combined to make lung cancer one of the most prevalent forms of the disease in the 21st century. Furthermore, lung cancer remains the most common cause of cancer-related death [1]. Early epidemiological studies using case–control methods showed that cigarette smoking was strongly associated with the risk of lung cancer. Active and passive smoking accounts for almost 90% of all cases of lung cancer, while the remaining cases are attributed to other agents such as radon in underground mines and outdoor
consumption of carcinogens [2]. In contrast, higher levels of leisure-time PA may have a protective effect against lung cancer [3].

Although there has been a gradual decline in the incidence of lung cancer in men, it continues to increase in women [1], so that overall incidence is rising. Furthermore, deaths from lung cancer in women surpassed those due to breast cancer in 1987 and accounted for approximately 26% of all female cancer deaths in 2006, compared to 31% in men [3]. Generally lung cancer causes more deaths than the next four most common cancers combined (colon, breast, pancreas cancers and PCa) [4], and despite many aggressive treatment strategies, survival has not changed in the last two decades.

In this chapter, we provide a brief overview of lung cancer and its treatment before presenting a rationale for pulmonary rehabilitation in lung cancer patients, focusing on exercise intolerance and a reduced QoL before and after radical treatment of lung cancer. Finally, we summarise current knowledge about the effects of exercise-based rehabilitation programmes before and/or after (surgical) treatment for the disease.

10.2 Classification of Lung Cancer

Lung cancer occurs in multiple histological types, as classified by conventional microscopy. It is generally divided into NSCLC and SCLC, with SCLC representing 10–15% of all cases [5]. The three major NSCLC subtypes include squamous cell carcinoma, adenocarcinoma and large cell carcinoma [6]. Despite extensive research the mechanisms underlying these different types of lung cancer remain uncertain. At the present time, there is an epidemiological trend towards an increase in the incidence of adenocarcinoma in comparison to the squamous cell carcinoma and small cell carcinoma [6, 7]. There is also strong evidence of association between environmental factors like smoking and certain types of lung carcinoma.

10.3 Presenting Symptoms of Lung Cancer

The initial presentation of lung cancer can be divided into two major categories, respiratory-related and constitutional or metastases-related symptoms. Respiratory symptoms include cough as the most frequent symptom but dyspnoea, chest pain and haemoptysis are also common. Other symptoms such as anorexia, weight loss and fatigue are usually related to tumour spread and often suggestive of a metastatic disease [8].

10.4 Diagnosis and Staging of Lung Cancer

Accurate staging is important in the evaluation of patients with lung cancer in order to determine appropriate therapy and prognosis. NSCLC sub-types are preferably treated with surgical intervention, depending on disease stage and localization. This
is in contrast to SCLC, as this tumour type grows rapidly, with early and widespread dissemination of the tumour being common at the time of initial diagnosis. Patients exhibiting this stage of the disease are mainly treated by chemotherapy.

It is now generally recognised that in addition to the histological classification of lung cancer, prognosis mainly depends on the anatomical extent of the tumour and which therapeutic options are possible [9]. In patients with SCLC, staging is simply classified into limited or extensive disease, depending on the lymphatic and distant spread of the tumour. In patients with NSCLC, however, staging is based on the tumour, node, metastasis (TNM) classification system, which is an upgrading system based on the local and regional spread of the tumour, from early stages (IA, IB, IIA, and IIB) to advanced stages (IIIA and B and stage IV) [10].

10.5 Medical Treatment of Lung Cancer

Despite major advances in understanding and treating lung cancer, the overall 5-year survival rate is 14% for NSCLC and 3% for SCLC [11]. Treatment of lung cancer depends on disease stage and includes surgery, RT and/or chemotherapy. The general conditions of the patient and his/her cardiopulmonary reserve, in addition to stage of the disease, are important factors determining the optimal therapeutic options [12]. Surgery is generally the treatment of choice for lung cancer, but in the majority of patients, the disease is already advanced at the time of diagnosis and hence, other forms of therapy can be of greater importance for reducing morbidity and improving QoL.

10.5.1 NSCLC Treatment for Early Stage and Localised Disease

Patients with stage I or stage II lung cancer are considered to have an early stage disease. Unfortunately these two stages combined account for only 25–30% of all patients with lung cancer [13]. When there is no medical contra-indication, surgery is the treatment of choice for stage I and II NSCLC [13]. Depending on the patient’s medical condition, lobectomy or greater resections are preferred to sub-lobular resection such as wedge resection and segmentectomy [14]. Video-assisted thoracic surgery is increasingly being used and is an acceptable alternative to open thoracotomy, with less peri- and post-operative morbidity and mortality [15]. Since distant recurrence is common after complete resection, chemotherapy may be used post-operatively as a complementary treatment, especially in patients with stage II disease. At the moment there is little evidence for the benefit of post-operative chemotherapy in stage IB disease [16].

10.5.2 Treatment for Loco-Regional Advanced Disease

About one third of patients diagnosed with NSCLC present with loco-regional involvement [10]. This means that the tumour has spread out of the confines of the
lung into surrounding structures but without clinical evidence of further dissemination. The overall 5-year survival rate for loco-regional advanced lung cancer is only 16% [10]. In the past decade, meta-analyses have gradually shifted the standard of care in selected patients with stage III NSCLC from radical local treatment only, to sequentially administered systemic and loco-regional treatments, to the present concurrent chemo-RT [17].

10.5.3 Treatment for Advanced and Metastatic Disease

About 40% of patients with newly diagnosed NSCLC present at an advanced stage, including patients with metastatic disease and those with locally advanced disease with malignant pleural or pericardial effusion [18, 19]. These patients are generally considered to be incurable, they have poor prognosis with a median survival time of 8–10 months and a 1-year survival rate of 30–35% [20]. Performance status at the time of the diagnosis and pre-treatment weight loss are important predictors of survival [21]. Chemotherapy improves survival and palliates symptoms, thereby improving the QoL in patients with stage IV NSCLC. The duration of first-line chemotherapy in patients with stage IV NSCLC should be brief, consisting of 3–4 cycles [22]. However, the response to first-line chemotherapy is generally short lived, with progression occurring on average 4–6 months after treatment is discontinued.

10.5.4 Treatment of Small Cell Lung Cancer

Because SCLC is a systemic disease from the onset in the overwhelming majority of patients, chemotherapy has become an essential part of the treatment. However, a meta-analysis conducted in 2006 [23] comparing different timings of chest RT showed a significantly higher 5-year survival when chest RT was started within 30 days after the start of chemotherapy. As brain metastases are common in patients with SCLC, prophylactic brain irradiation has been performed in patients with either limited or extensive disease, especially in those who achieve a complete response following chemotherapy [24]. A meta-analysis of randomised trials of prophylactic brain irradiation in patients with complete response concluded that it significantly reduced central nervous system failure and produced a modest but significant improvement in median survival [25].

10.6 Pulmonary Rehabilitation

Recently, pulmonary rehabilitation has been defined by the American Thoracic Society and the European Respiratory Society as an evidence-based, multidisciplinary and comprehensive intervention for patients with chronic respiratory
diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualised treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimise functional status, increase compliance and reduce health-care costs by stabilizing or reversing the systemic manifestations of the disease. Pulmonary rehabilitation programmes involve patient assessment, exercise training, education, nutritional intervention and psychosocial support. In a broader sense, pulmonary rehabilitation includes a spectrum of intervention strategies integrated into the lifelong management of patients with chronic respiratory disease and involves a dynamic, active collaboration between the patient, family and health-care providers. This strategy addresses both the primary and the secondary impairments associated with respiratory disease [26].

To date, the effects of (exercise-based) pulmonary rehabilitation programmes have mainly been studied in patients with moderate to very severe COPD [27]. Comprehensive pulmonary rehabilitation programmes of 8 weeks or longer have been shown to improve QoL and functional mobility in clinically stable patients with moderate to very severe COPD, without significant improvements in the impaired pulmonary function. For example, mean differences in changes between pulmonary rehabilitation and the usual-care control group in breathlessness (mean ES 1.06, 95% CI 0.85–1.26 points per question), fatigue (0.92, 0.71–1.13), emotional function (0.76, 0.52–1.00) and mastery of complaints (0.97, 0.74–1.20), as assessed with the Chronic Respiratory Disease Questionnaire [27], exceeded the minimum clinically important difference of 0.5 points per question on a seven-point scale [28]. Thus, pulmonary rehabilitation can be considered as a powerful non-pharmacological intervention and has become an integrated part of the management of patients with chronic lung disease, particularly in patients with moderate to very severe COPD [29].

Surprisingly, the effects of exercise-based rehabilitation in patients with other chronic lung diseases have not been extensively studied [26, 30, 31]. Nevertheless, the American Thoracic Society and the European Respiratory Society advocate the use of pulmonary rehabilitation in patients with non-COPD lung disease, irrespective of age, gender, lung function and smoking status [26].

10.6.1 Rationale for Pulmonary Rehabilitation in Lung Cancer Patients

10.6.1.1 Pre-operative Exercise Intolerance

The pre-operative physical condition of lung cancer patients is generally poor [32]. It is not known to what extent this is influenced by physical inactivity, but lung cancer patients are known to have daily symptoms of dyspnoea and/or fatigue [33]. Physical deconditioning may be of clinical relevance in the post-operative phase. A strong inverse correlation between objective pre-operative exercise capacity (treadmill testing) and post-operative length of stay in hospital has been reported in lung
cancer patients, even after correcting for confounding factors like gender, smoking history, pre-operative degree of dyspnoea and the type of surgery [34]. Indeed, patients with a prolonged post-operative hospital stay (>10 days) failed to exceed an exercise intensity equivalent to seven METs during their pre-operative exercise test. This is in accordance with a study reported by Epstein et al. [35], which showed that an inability to perform an exercise test predicts increased cardiopulmonary morbidity and mortality after lung resection. Moreover, patients with resectable lung lesions who were deemed to be inoperable on the basis of their poor pre-operative pulmonary function and/or hypercapnia, tolerated the lung resection well when their pre-operative peak aerobic capacity was >15 ml.kg⁻¹ min⁻¹ [36]. Interestingly, pre-operative peak aerobic capacity was not related to spirometric impairments [36], suggesting that extra-pulmonary features, like skeletal muscle dysfunction, contribute to the poor exercise performance [37]. Indeed, a majority of the patients who had to undergo a lobectomy (70%) or pneumonectomy (69%) were not able to continue their pre-operative peak exercise treadmill test because of leg discomfort [38]. So, there is a clear rationale for offering lung cancer patients with a poor pre-operative exercise performance a pre-operative exercise-based pulmonary rehabilitation programme to improve exercise tolerance and, in turn, possibly reduce post-operative complications and length of hospital stay [39].

10.6.1.2 Peri- and Post-operative Exercise Intolerance

Surgical and non-surgical treatment of lung cancer can reduce patients’ peak exercise performance. Nagamatsu et al. [40] reported that it takes 1 year of recovery for peak aerobic capacity to return to pre-operative levels, although mean peak aerobic capacity for the cohort of patients was still abnormally low (719 ml min⁻¹). In another study, Nezu et al. [41] reported a lower peak aerobic capacity more than 6 months after a lobectomy (−13%) or pneumonectomy (−28%) compared to pre-operative values, suggesting that the amount of lung resected may, at least in part, determine the decline in post-operative peak aerobic capacity. However, the post-operative reduction in peak aerobic capacity was not related to the number of subsegments resected [41]. Other research has also shown that the change in pulmonary function only partially explains the variance in decline of peak aerobic capacity following lung resection [42] and subjective post-operative exercise after lobectomy can be limited by leg discomfort more than 6 months after surgery [38]. These findings again support the addition of an exercise-based pulmonary rehabilitation programme to the management of post-operative lung cancer patients. In addition to the positive impact that exercise-based pulmonary rehabilitation could have on cardiopulmonary function in the post-operative period, its potential role for evoking localised skeletal muscle adaptations (and the impact that this could have on skeletal muscle endurance capacity) should also be considered.
10.6.1.3 Peri- and Post-operative Quality of Life

Lung cancer patients eligible for lung resection have a worse pre-operative QoL compared with the general healthy population [43, 44], and a reduction in QoL has been observed to persist for at least 6 months following surgery [44]. Schulte et al. [45] recently studied the long-term effects of low-volume parenchymal resection (lobectomy) or high-volume parenchymal resection (pneumonectomy) on QoL in 159 NSCLC patients. The European Organisation for Research and Treatment of Cancer QoL-30 questionnaire was administered pre-operatively, before discharge from the hospital, and at 3, 6, 12 and 24 months after the baseline assessment. QoL dropped significantly below the baseline values after discharge from the hospital and recovered somewhat in the 6 months after discharge but remained below pre-operative levels. It took 2 years for QoL to recover to pre-operative levels [45] but even then the 24-month assessment showed that QoL remained below normative values for healthy individuals. Moreover, daily symptoms of dyspnoea remained present throughout the 24 months and never reached pre-operative levels [45]. As pulmonary rehabilitation has been shown to improve QoL and daily symptoms in patients with clinically stable COPD [27] and directly after hospital discharge following an acute exacerbation [46], there is a clear rationale for starting pulmonary rehabilitation in lung cancer patients as soon as possible after surgical treatment.

10.6.2 Evidence for the Impact of Exercise Rehabilitation Before Surgical Treatment

Recently, Jones et al. [47] studied the effects of a pre-operative exercise-based rehabilitation programme in 20 consecutive deconditioned (mean baseline aerobic capacity of 15.7 ml.kg⁻¹ min⁻¹) patients with suspected stage I to IIIA NSCLC who were candidates for primary surgery with curative intent. Patients underwent a supervised exercise training programme which was specifically aimed at increasing peak aerobic capacity, involving five cycle ergometry sessions per week on consecutive days until surgical resection. The exercise intensity was initially set at 60% of the baseline peak aerobic capacity for a duration of 20 min. The duration and/or intensity being subsequently progressed to 30 min at 65% of peak aerobic capacity. From the fourth week onwards, patients performed three sessions at 65% of the peak aerobic capacity, one ventilatory threshold session for 20–30 min and one interval session. Interval sessions consisted of 30 s at peak aerobic capacity followed by 60 s of active recovery for 10–15 intervals. A 15–22% improvement in peak aerobic capacity was observed following the exercise-based rehabilitation programme [47]. Unfortunately, post-operative values worsened again. In fact post-operative peak aerobic capacity 50 days after lung resection was not significantly different from baseline pre-operative values [47]. Even though these results are better than the previously reported decline of about 25% in peak aerobic capacity in
the first 3 months after surgery, the need for post-operative exercise rehabilitation is highlighted.

Bobbio et al. [39] also showed that short-term pre-operative pulmonary rehabilitation programmes can improve exercise tolerance (peak aerobic capacity: +21% of baseline values) in 12 patients with COPD who were candidates for lung resection (due to NSCLC), but without improving the impairment of pulmonary function. After a smoking cessation programme and optimal pharmacological treatment, patients were eligible to start the 4-week exercise-based pulmonary rehabilitation programme, consisting of a daily 1.5 h hospital appointment, 5 days a week for 4 weeks. During the first session, physical modality therapy (including instruction on controlled breathing and cough techniques) was implemented. The patients were also instructed in incentive spirometry exercises and were asked to repeat the exercises twice daily at home. The exercise training programme consisted of aerobic exercise on a leg cycle ergometer, with each session consisting of a 5-min warm-up at 30% of the pre-determined peak power output, followed by 30 min at 50% of peak power output and ending with a 5-min cool down. Cycling load was progressively increased weekly up to 80% of the baseline peak power output. At the end of each aerobic exercise session, patients underwent muscle stretching for 10 min and the session was completed with upper extremity and trunk muscle free weights exercises. Trained medical staff and physical therapists supervised patients during all sessions. This study showed that exercising at moderate to high intensities is feasible for lung cancer patients who are eligible for lung resection.

10.6.3 Evidence for the Impact of Exercise Rehabilitation After Surgical Treatment

10.6.3.1 Conventional Exercise Modalities

Spruit et al. [48] and colleagues were one of the first groups to show that patients surgically treated for lung cancer (mostly diagnosed with NSCLC) may be good candidates for pulmonary rehabilitation. In a non-randomised, clinical pilot study, the effects of a multidisciplinary inpatient rehabilitation programme on pulmonary function, 6-min walking distance and peak cycling power output were studied in 10 patients recruited by their chest physician at the outpatient clinic a median of 3 months after completing intensive lung cancer treatment. The majority of patients had one additional earlier diagnosed comorbidity (COPD, arterial hypertension or transient ischemic attack) or had previously undergone invasive medical treatment (percutaneous transluminal coronary angioplasty or hysterectomy). None of the patients had participated in any form of exercise training in the 6-month period before initiating the rehabilitation programme.

Exercise training, consisting of daily cycle ergometry, treadmill walking, weight training and gymnastics, comprised the main component of the multidisciplinary rehabilitation programme. Cycle ergometry was initially performed for 20 min at
60% of the baseline peak cycling load, and treadmill walking was performed for 20 min at 80% of the baseline walking speed. Weight training for skeletal muscle groups of the upper (chest press, lat pulley and vertical traction) and lower extremities (leg press, leg curl, hip adduction, hip abduction and leg extension) was performed for 3 × 15 repetitions at 60% of the one-repetition maximum load. Patients also participated in 30 min of gymnastics, which focused on general mobilization and flexibility exercises. The intensity of cycle ergometry, treadmill walking and weight training was progressed over time, on the basis of Borg symptom scores for dyspnoea and/or fatigue (target scores: 4–6 on a 10-point scale) to maintain the same relative perceived training load during the intervention period of 8 weeks [49–51]. Exercise training was performed under the close supervision of a physical therapist in a rehabilitation setting involving inpatients with severe COPD. An occupational therapist, dietician, behavioural scientist and respiratory nurse specialist were also available for consultation if required. Baseline exercise performance was poor (median 6-min walking distance 64% predicted and median peak cycling load 59% predicted). Eight weeks after the baseline assessment, the impairment of pulmonary function was unchanged, while significant improvements were found in the 6-min walking distance (median change +145 m; +43% of baseline) and peak cycling power output (+26 W; +34% of baseline).

Jones et al. [52] also reported positive effects of a supervised exercise-based pulmonary rehabilitation programme in 19 lung cancer patients using a prospective, single-group design. The intervention consisted of three individually tailored aerobic cycle ergometer sessions per week on non-consecutive days for 14 weeks. Initial exercise intensity was set at 60% of the baseline peak power output for a duration of 15–20 min. Duration and/or intensity were subsequently increased throughout weeks 2–4 up to 30 min at 65% peak power output. In weeks 5–6, the exercise intensity varied between 60 and 65% of peak power output for a duration of 30–45 min for two sessions and in the remaining session, patients cycled for 20–25 min at ventilatory threshold intensity. From week 7 onwards, patients performed two sessions at 60–70% peak power output, with one ventilatory threshold session for 20–30 min. Finally, in weeks 10–14, patients performed two sessions at 60–70% peak power output, with one interval session. Interval sessions consisted of 30 s at peak power output, followed by 60 s of active recovery for 10–15 intervals. Jones et al. reported significant improvements in QoL, exercise performance and fatigue, particularly among patients not receiving chemotherapy [52].

Cesario et al. [53] were the first group to design a non-randomised controlled clinical trial to assess the effects of a post-operative pulmonary rehabilitation programme in NSCLC patients who had undergone lung resection. Of the 211 eligible patients who had been offered the inpatient pulmonary rehabilitation programme, 25 patients accepted and were included in the study and the remaining 186 patients acted as the control group. The rehabilitation team consisted of a chest physician director, physical therapists, nurses, a psychologist and a dietician and the programme was undertaken by patients admitted to a 28-bed ward. Patients participated in five supervised sessions of 3 h each week, up to a maximum of 20 during a hospital stay of 26 ±3 days. The programme included supervised incremental
exercise until the patient could achieve 30 min of continuous cycling at 70–80% of the pre-determined peak power output. Abdominal muscle activities, inspiratory resistive sessions, treadmill walking, upper and lower extremity exercise training and full-arm circling were also applied. Educational sessions were conducted twice weekly and covered topics like pulmonary pathophysiology, the pharmacology of patient medications, dietary counselling, relaxation and stress management techniques, energy conservation principles and breathing retraining. The 6-min walking distance decreased in the control group (from 499 to 467 m, *p* < 0.01). In contrast, a significant improvement was observed in the rehabilitation group from 298 to 393 m despite there being no change in pulmonary function.

Improvements in functional and peak exercise capacity in lung cancer patients, without change in pulmonary function may seem surprising but is consistent with the findings of previous research. Improved skeletal muscle function and/or changes in skeletal muscle metabolism may at least partially explain the change in exercise performance following post-operative rehabilitation. Indeed, skeletal muscle dysfunction has been shown to be related to exercise intolerance in patients with COPD and chronic heart failure, independent of the respective level of pulmonary or cardiac impairment [54–56]. Moreover, skeletal muscle function improves following a rehabilitation programme in patients with other chronic lung diseases [30, 57, 58]. Unfortunately, the impact of exercise rehabilitation on skeletal muscle function/metabolism has never been studied in lung cancer patients.

### 10.6.3.2 Neuromuscular Electrical Stimulation

Most exercise-based pulmonary rehabilitation programmes consist of conventional exercise interventions, like endurance training and/or resistance training [31], but these exercise modalities can evoke severe symptoms of dyspnoea [59]. Thus, there is substantial interest in exercise training strategies that do not evoke dyspnoea, such as transcutaneous NMES [60]. NMES is the application of an electrical current through electrodes placed on the skin over the targeted muscles, thereby depolarizing motor neurons and, in turn, inducing skeletal muscle contractions [61]. It has been shown to be effective in patients with very severe COPD and chronic heart failure [62].

Recently, Crevenna et al. [63] were the first group to study the effects of NMES in a patient with metastatic lung cancer and brain secondaries. Fatigue and limited functional mobility and, in turn, a poor QoL are common side-effects of advanced metastatic tumours [64]. The NMES protocol, aimed at increasing muscle strength and endurance, was applied through adhesive surface electrode patches attached to the skin of the gluteal muscles and knee extensors of both legs. The intervention lasted for 4 weeks and comprised of 20 sessions of one 30-min NMES treatment to the gluteal muscles and one 30 min NMES treatment to the knee extensors. No adverse events were reported and compliance to the sessions was 100%. Impressive improvements in 6-min walking distance (from 420 to 603 m) and QoL were reported. The Short-Form 36 health survey domain of ‘physical functioning’ increased from 45 to 80 points, the ‘role physical’ domain increased from 50 to
100 points and the ‘vitality’ domain increased from 30 to 60 points [65]. However, Crevenna and colleagues only presented a single case report and there were some methodological limitations [66]. Nevertheless, this preliminary evidence suggests that NMES may be a worthwhile intervention for severely disabled lung cancer patients but randomised controlled trials are needed to study efficacy and safety issues in this patient group.

10.7 Future Recommendations

To date, the number of peer-reviewed trials that have studied the effects of pre-, peri- and post-operative exercise-based rehabilitation programmes in lung cancer patients is limited. Moreover, existing trials have small sample sizes and/or utilised non-randomised controlled designs and patient selection bias may therefore exist [32, 47]. Evidence suggests that an improved peak aerobic capacity following pre-operative exercise-based rehabilitation programmes may increase the number of candidates eligible for curative-intent pulmonary resection [39] and might reduce the number of peri-operative complications but more research is needed to verify this. In the peri- and post-operative phase, more well-designed, prospective, randomised controlled trials aimed at studying the effects of exercise-based pulmonary rehabilitation programmes, and which include long-term follow-up assessments and blinded outcome assessors, are warranted. The inclusion of a parallel non-exercising control group is necessary to determine how the effects of exercise rehabilitation compare with the natural post-treatment recovery process. A comprehensive interdisciplinary approach is imperative: in addition to exercise facilitators/physical therapists, this might consist of specialists in nutritional and psychosocial counselling, behaviour change, occupational therapy and progressive relaxation techniques [26, 67].

Future trials should also study the effects of NMES during and after cancer treatment(s) like chemotherapy and RT. The toxicity of these treatments can lead to reduced functional mobility, psychological impairments and severe debilitating fatigue [68], while NMES has been shown to improve dyspnoea and fatigue in severe chronic disease [62].

10.8 Summary and Conclusions

Lung cancer is one of the most prevalent types of cancer in Western societies. Pre-operative QoL and exercise capacity are poor and become worse following (surgical) treatment, and the natural recovery of QoL and exercise tolerance are only partial over extended periods of time. Therefore, in patients with lung cancer, there is a clear indication for comprehensive peri- and post-operative exercise-based rehabilitation. On the basis of current literature, it appears that these patients are good candidates for pulmonary rehabilitation programmes.
References


Chapter 11
Exercise and Cancer Mortality

John Saxton

Abstract  Nearly 25 million people are alive today after being diagnosed with cancer during the last 5 years. Despite these encouraging statistics, there is a need to more fully understand the impact of lifestyle-modifiable factors, such as PA on cancer mortality. To date, no randomised controlled trials have investigated the effects of PA on cancer-specific mortality or all-cause mortality in cancer survivors. However, a number of prospective cohort studies have reported negative associations between PA and cancer mortality. The most compelling observational evidence of the survival benefits to be gained from a physically activity lifestyle has emanated from studies of post-diagnosis PA in breast and colorectal cancer survivors. These studies have shown clear inverse associations between post-diagnosis PA and survival, with the benefits being independent of age, gender, obesity and disease stage at diagnosis. Three of the four cohort studies of breast cancer survivors showed that women who are achieving the equivalent of 30 min of moderate intensity PA on five or more days of the week can halve their risk of mortality up to 8 years of follow-up. For colorectal cancer survivors, current evidence suggests that higher levels of PA are required to achieve similar benefits. Habitual exercise might also have a role to play in retarding PCa progression and in counteracting the increased risk of CV mortality in PCa patients. However, there is a need for further studies of other cancer populations and randomised controlled trials to provide more robust data on the frequency, intensity, duration and type of PA which confers the greatest survival benefits to patients recovering from different forms of cancer and associated treatments.
11.1 Introduction

Worldwide, there are 6.7 million deaths from cancer each year [1]. Although the global 5-year mortality rate for some cancers (notably lung cancer) remains high, survival statistics for many other common cancers are improving. It is estimated that 24.6 million people are alive today in the world after being diagnosed with cancer during the last 5 years [1]. A recent report showed that the 5-year survival rates in Europe for breast, prostate and colon cancer are now in excess of 70, 55 and 45%, respectively [2]. In North America, Australasia and Japan, survival rates are approximately 10% higher than this for breast and colorectal cancer and the 5-year survival rate for PCa it is particularly high in North America (91%) and Australasia (77%). Despite these encouraging statistics, there is a need to more fully understand the impact of lifestyle-modifiable factors, such as PA, on cancer mortality. Individuals who have been treated for cancer are at risk of cancer recurrence. They are also at increased risk of developing new primary malignancies and other chronic disease conditions such as CV disease, diabetes mellitus and osteoporosis [3]. A growing body of evidence supports the positive effect of PA on physical functioning, CV health and QoL in cancer survivors but evidence for the impact of PA on disease-free survival and mortality is limited. The following are the key research questions:

- Can habitual exercise after a cancer diagnosis improve disease-free survival and mortality?
- Are any observed positive effects of a physical active lifestyle restricted to individuals who have been active throughout their lives or at least in the years before the cancer diagnosis?
- Are any observed benefits of post-diagnosis exercise participation independent of other prognostic risk factors such as obesity?
- What frequency, intensity, duration and type of exercise has the greatest impact upon disease-free survival and mortality after a cancer diagnosis?
- Which specific cancer types can benefit the most (in terms of mortality and disease-free survival) from a physically active lifestyle?

To date, no randomised controlled trials (RCTs) have investigated the effects of PA on cancer-specific mortality or all-cause mortality in cancer survivors. Hence, a causal link between PA and mortality in cancer survivors cannot be established from the evidence that is currently available. However, large-scale prospective cohort studies have investigated associations between self-reported PA levels (or cardiopulmonary fitness as a surrogate measure of PA status) and cancer mortality in men and women. These studies are useful for providing estimates of mortality risk associated with different levels of PA (or cardiopulmonary fitness) but they do have some inherent limitations. Notably, questionnaire and interview techniques for assessing self-reported PA are susceptible to recall bias and hence, misclassification errors. Moreover, PA data are sometimes only assessed for a ‘snap-shot’ in time, with no indication of whether this is maintained through the follow-up period. However, this method of data collection is highly pragmatic for large population
studies, and in some instances, the researchers have validated the questionnaires with objectively assessed PA data. Additionally, in most of the studies, RRs were determined after adjusting for other factors which are predictive of cancer survival and the multivariable adjusted HR or RR is reported.

11.2 Evidence from Prospective Cohort Studies

A number of different approaches have been used to investigate the association between PA status and cancer mortality. In Section 11.3, prospective cohort studies that have investigated associations between cardiopulmonary fitness or PA levels and future cancer mortality are presented. In some of the studies, cardiopulmonary fitness (surrogate for PA status) was assessed in initially healthy individuals at baseline, with RR estimates for overall cancer mortality being based on a comparison between the relatively fit and unfit members of the cohort during a defined period of follow-up. In other studies, PA levels were assessed in apparently healthy individuals at baseline, before cancer mortality was compared between the physically active and most sedentary individuals during the follow-up period. The main limitation of this type of design is the difficulty in distinguishing whether any observed inverse associations between cardiopulmonary fitness or PA and cancer mortality are linked to reductions in cancer occurrence, influence on stage of cancer at diagnosis or impact of post-diagnosis PA on cancer survival. However, as the latter is highly relevant to individuals who have been diagnosed with cancer, consideration of these studies is justified. In addition, it is unclear at what time-points during the lifespan PA would have the greatest benefits (in terms of post-diagnosis cancer survival). Hence, knowledge of how pre-diagnosis PA levels is associated with future overall cancer mortality could inform the interpretation inverse associations between post-diagnosis PA and cancer mortality.

In Sections 11.4 and 11.5, prospective cohort studies that have investigated PA levels in breast and colorectal cancer survivors are discussed. The association between PA and mortality in breast and colorectal cancer patients has been assessed in a number of different ways. Some studies have investigated the association between pre-diagnosis PA status and mortality by asking patients to recall typical PA levels at some defined time-point before being diagnosed with cancer. More informative studies, however (presented in Section 11.5), have assessed PA levels at some time-point after diagnosis of breast or colorectal cancer, before deriving the RR of mortality from a comparison of death rates between the physically active and the least active survivors. Two studies investigated both pre- and post-diagnosis PA status in relation to mortality, as well as assessing the impact of a change in PA status from pre- to post-diagnosis on mortality risk. These latter studies have yielded the most convincing observational evidence to date of an inverse association between post-cancer diagnosis PA and disease-free survival. Finally, this chapter considers the potentially important influence of PA on PCa progression and mortality using evidence from primary prevention studies. In addition, the possible impact of PA on CV mortality in PCa patients is discussed.
11.3 Cardiopulmonary Fitness, Physical Activity and Overall Cancer Mortality in Initially Healthy Individuals

11.3.1 Is Cardiopulmonary Fitness Associated with the Risk of Future Cancer Mortality?

Using data from the Cooper Clinic in Dallas, Steven Blair and colleagues [4] were one of the first groups to report a strong inverse gradient between cardiopulmonary fitness and overall death rates for cancer. Since then, a number of large-scale North American prospective cohort studies of initially health adults (at the baseline assessment) have reported associations between cardiopulmonary fitness (surrogate of PA status) and future cancer mortality. Some studies graded participants by quintiles of cardiopulmonary fitness and derived RR estimates of mortality by comparing cancer death rates in the lowest quintile (reference group) with all others. At least two of these studies showed a stronger relationship between physical fitness and cancer mortality for men in comparison to women [5, 6] but from the reports it was not possible to establish the actual fitness levels of the different quintiles. In other studies, cardiopulmonary fitness was more precisely quantified. For Example, Laukkanen et al. [7] showed that cardiopulmonary fitness had a strong inverse association with non-CV disease-related mortality in men, primarily due to cancers and pulmonary diseases. Men aged 42–61 years with low cardiopulmonary fitness ($\dot{V}O_2$ max $< 27.6$ ml kg$^{-1}$.min$^{-1}$) had more than a twofold increased risk of non-CVD-related mortality over an average follow-up period of 10.7 years in comparison to men in the highest cardiopulmonary fitness category ($\dot{V}O_2$ max $> 37.1$ ml kg$^{-1}$.min$^{-1}$). Another group showed that high (equivalent to a $\dot{V}O_2$ max of 47 ml kg$^{-1}$.min$^{-1}$) and moderate (equivalent to a $\dot{V}O_2$ max of 38 ml kg$^{-1}$.min$^{-1}$) levels of cardiopulmonary fitness in men were associated with risk reductions for smoking-related and non-smoking-related cancer mortality in the range of 34–66% over an average of 10 years of follow-up, when compared to the least fit men (equivalent to a $\dot{V}O_2$ max of 31 ml kg$^{-1}$.min$^{-1}$). Risk reductions of 55 and 38% for total cancer mortality, respectively, were observed in the high and moderately fit men in relation to the least fit men [8]. There is also evidence that the risk reductions for cancer mortality that are associated with increased cardiopulmonary fitness extend to Asian cultures. Initially healthy Japanese men in the highest cardiopulmonary fitness quartile ($\dot{V}O_2$ max of 46 ml kg$^{-1}$.min$^{-1}$) at the baseline assessment had a 59% reduced risk of cancer mortality over a mean follow-up period of 16 years in comparison to men in the lowest quartile ($\dot{V}O_2$ max of 29.8 ml kg$^{-1}$.min$^{-1}$) [9].

Two recent studies conducted by researchers at the Cooper Clinic in Dallas, USA, used data from the Aerobics Center Longitudinal Study to investigate associations between the cardiopulmonary fitness and the risk of breast and digestive system cancers [10, 11]. Digestive system cancers were defined as all cancers of the alimentary tract below the neck [10]. In the first of these studies involving nearly 15,000 women aged 20–83 years, those in the highest cardiopulmonary fitness category at the baseline assessment (equivalent to a $\dot{V}O_2$ max of 39 ml kg$^{-1}$.min$^{-1}$) had a
55% reduced risk of breast cancer mortality in comparison to the least fit women (equivalent to a $\dot{V}O_2$ max of 23 mlkg$^{-1}$min$^{-1}$) over a mean follow-up period of 16.4 years [11]. Furthermore, an aerobic exercise capacity >10 METs (equivalent to a $\dot{V}O_2$ max of 35 ml.kg$^{-1}$ min$^{-1}$) was associated with nearly a threefold reduced risk of breast cancer mortality in comparison to women with an aerobic exercise capacity of <8 METs (equivalent to a $\dot{V}O_2$ max of 28 ml kg$^{-1}$ min$^{-1}$). In the second study involving nearly 39,000 men aged 20–88 years, those in the moderate (equivalent to a $\dot{V}O_2$ max of 37 ml kg$^{-1}$ min$^{-1}$) and high (equivalent to a $\dot{V}O_2$ max of 48 ml kg$^{-1}$ min$^{-1}$) cardiopulmonary fitness categories had a 37 and 49% reduced risk of digestive system cancer mortality, respectively, in comparison to the least fit group (equivalent to a $\dot{V}O_2$ max of 30 ml kg$^{-1}$ min$^{-1}$) [10]. Sub-group analyses also revealed evidence of reductions in the risk of colon cancer mortality (–39%), colorectal cancer mortality (–42%) and liver cancer mortality (–72%) in those with moderate or high levels of cardiopulmonary fitness in comparison to the low fitness group. Interestingly, an additional study of the same cohort reported a dose–response association between muscular strength and risk of total cancer mortality in men, which was largely independent of BMI, percentage body fat, waist circumference or cardiopulmonary fitness. Reductions in the risk of digestive system mortality were also observed in the strongest men versus those with the lowest levels of muscular strength.

Although a Canadian study did not find any significant association between cancer mortality and physical fitness over a 7-year follow-up period [12], the balance of available evidence suggests that for men, higher levels of cardiopulmonary fitness are associated with some level of protection against cancer mortality within the follow-up periods studied (up to 16 years). For women, although recent evidence for breast cancer mortality is encouraging [11], more studies are needed before similar conclusions can be drawn.

### 11.3.2 Is Physical Activity Associated with the Risk of Future Cancer Mortality?

Two recent studies have suggested that current PA guidelines of at least 30 min of moderate intensity PA on at least 5 days of the week [13, 14] are associated with a reduced risk of future cancer mortality. Leitzmann et al. [15] reported that 1–3 h of moderate intensity PA per week was associated with a 14% risk reduction of future cancer mortality in initially healthy men and women at the baseline assessment (versus inactive men and women), whereas no extra benefit was associated with higher volumes of moderate intensity PA. This evidence was recently supported by Orsini et al. [16], who showed that men who walked or bicycled an average of 30 min.day$^{-1}$ had a 34% reduced risk of cancer mortality in comparison to sedentary men. The benefits of a moderately activity lifestyle on cancer mortality are also observed in Asian cultures. Inoue et al. [17] reported a 24% risk reduction for cancer mortality in Japanese men and a 35% risk reduction in Japanese women who were expending
at least 35 MET-h.day$^{-1}$ of total PA over an average follow-up period of 8.7 years [17]. It is difficult to compare associations for total PA (expressed in MET-h.day$^{-1}$) to other studies which have assessed only recreational or leisure-time PA in units of MET-h.week$^{-1}$. Nevertheless, further analysis of the data showed that leisure time sports or PA performed on 1–2 days.week$^{-1}$ was associated with risk reductions of 25–31% for all-cause mortality in men and women, with cancer mortality accounting for 44 and 47% of all deaths, respectively [17].

Other studies have investigated the impact of vigorous PA participation on future cancer mortality in initially healthy individuals at the baseline assessment. A British cohort study showed that men who regularly engaged in vigorous (or moderate intensity) PA had a 41% risk reduction for total cancer mortality over 9.5 years of follow-up in comparison to inactive men [18]. This was mainly associated with a reduced risk of digestive tract and lung cancer but not cancers at other sites. A large Finish population-based cohort study also reported risk reductions in the range of 21–27% for cancer mortality in men and women who performed at least 3 h.week$^{-1}$ of vigorous PA over an average follow-up period of 17.7 years [19]. In the previously cited study of Leitzmann et al. [15], further analysis of the PA data showed that 3–4 sessions of vigorous PA per week (of at least 20 min duration) was associated with slightly greater risk reductions for cancer mortality (18%) than were observed for 1–3 h of moderate intensity exercise per week.

Not all studies have reported significant inverse associations between habitual exercise and future cancer mortality. For example, there was no evidence that the risk of death due to cancer was related to higher PA levels in a Canadian population over a 7-year follow-up period [12]. Another recent large-scale Canadian cohort study reported no association between regular sedentary behaviour (assessed as ‘sitting time’ during the course of most days) and future cancer mortality [20]. In addition, a significant inverse association between PA and cancer mortality was only observed for men but not women in data from the Cooper Clinic in Dallas, USA [5]. In the latter study, however, the smaller number of deaths in women across different PA quartiles might have reduced the statistical power to detect significant associations. However, in accordance with studies of cardiopulmonary fitness, the weight of available observational evidence suggests that fairly modest amounts of moderate or vigorous PA are associated with risk reductions for cancer mortality within the follow-up periods studied (up to 18 years).

### 11.4 Pre-diagnosis Physical Activity and Mortality in Breast and Colorectal Cancer Survivors

Five prospective cohort studies have investigated the association between pre-diagnosis PA levels and breast cancer mortality in breast cancer survivors. Rohan et al. [21] assessed pre-diagnostic recreational PA in a cohort of 451 Australian women who were between the ages of 20–74 years at diagnosis. The participants were asked to report the number of hours each week that they had spent undertaking
light, moderate and vigorous recreational activities during the year before diagnosis and each intensity level was converted into energy expenditure per week. The average time interval between diagnosis and interview was 4.8 months and the median duration of follow-up was 5.5 years. During this time, 112 of the patients died from breast cancer and 11 from other causes. This study revealed no evidence of an inverse association between total pre-diagnosis recreational activity and risk of breast cancer mortality. When risk of breast cancer mortality was examined by intensity of PA, this analysis (based on a restricted number of women) revealed only a non-significant inverse association between moderate intensity PA (>0 kcal.week\(^{-1}\)) and breast cancer mortality (multivariable adjusted HR: 0.51; 95% CI, 0.24–1.06). For vigorous intensity recreational PA (>0 kcal.week), a non-significant increased risk of breast cancer mortality was observed (multivariable adjusted HR: 1.75; 95% CI, 0.68–4.47). For the moderate and vigorous PA analysis, the data were only sufficient to allow comparisons of the risk of death between those who engaged in any PA at these intensity levels and those who did not. Additionally, self-reported PA levels might have been influenced by undiagnosed symptoms in the year prior to diagnosis.

In a second study, Borugian et al. [22] assessed recreational PA levels in 603 female breast cancer patients aged 19–75 years at diagnosis (an average of 2 months after surgery but before the start of adjuvant treatment). Participants were asked about the frequency of various recreational physical activities, including walking and stair climbing, from which the number of activities per week was calculated. This study had a longer follow-up period of 10 years, during which time there were 112 breast cancer deaths and 34 deaths due to other causes. No relationship was observed between the frequency of any PA variable and breast cancer mortality in this cohort and there were no trends in the data. However, in this study, self-reported PA levels might have been influenced by the physical condition of the women at the time of assessment.

A potential limitation of these two studies is the ‘snap-shot’ assessment of PA status, which may not have been typical of lifetime or current PA behaviour. In an attempt to overcome this limitation, three further prospective cohort studies assessed PA status at different time-points in the women’s lifespan. Enger et al. [23] assessed the number of hours per week of participation in all recreational activities, beginning with the year of each woman’s first menstrual period and ending at the reference date, defined as 12 months before breast cancer diagnosis. In this cohort of 525 younger women (aged ≤40 years), during a median follow-up time of 10.4 years, there were 251 breast cancer deaths and a further 12 deaths due to other causes. However, no clear association between self-reported lifetime recreational PA or higher levels of PA 12 months prior to diagnosis and risk of breast cancer mortality was observed. Only a non-significant trend for an inverse association was reported for women who had been physically active (0.1–3.7 h.week\(^{-1}\)) between the menarche and the reference date and who had maintained ≥1 h.week\(^{-1}\) up to the year preceding the reference date (multivariable HR: 0.61; 95% CI, 0.36–1.04). It was noted that the women in this study were among the youngest reported in the literature and as a group had a very low median BMI prior to diagnosis.
In a larger cohort of 1,264 younger women aged 20–54 years at diagnosis [24], participants were asked to recall the frequency of selected vigorous or moderate intensity recreational activities at the age of 12–13 years, 20 years, and the year before breast cancer diagnosis during interviews conducted a median of 4.2 months after diagnosis. Relative units of PA per week for each time period were derived from the product of frequency and intensity of PA. During a median of 8.5 years of follow-up (range, from 3 months to 9.8 years), 212 women died of breast cancer within 5 years of diagnosis and 285 women died overall within the follow-up period of the study. No statistically significant associations between breast cancer mortality and PA levels at the ages of 12–13 years or 20 years or in the year prior to diagnosis were observed. A non-significant trend for a 22% decrease in all-cause mortality was observed in women in the highest PA quartile compared with women in the lowest PA quartile in the year before diagnosis (multivariable adjusted HR: 0.78; 95% CI, 0.56–1.08). This risk reduction was doubled for the unadjusted estimate (unadjusted HR: 0.66; 95% CI, 0.46–0.92). Interestingly, when associations between mortality and PA in the year prior to diagnosis were modified by BMI, higher levels of PA were only associated with reduced risk of mortality among women who were overweight or obese (BMI ≥ 25 kg m–2 and/or waist:hip ratio >0.80) at the time of diagnosis. A limitation of this study is the method used to grade PA (relative PA units), which makes it difficult to estimate the amount of recreational PA that is required to achieve the observed potential benefits.

Another cohort study asked 1,225 women who had been diagnosed with breast cancer to recall typical lifetime PA behaviour, categorised into occupational, household and recreational PA [25]. In this Canadian cohort, over a minimum of 8.3 years of follow-up, there were 327 disease recurrences, progressions or new primary tumours and over a minimum follow-up period of 10.3 years, 223 breast cancer deaths and 118 deaths from other causes. A 34% reduced risk of disease recurrence, progression or a new primary tumour was observed in women who reported a lifetime moderate intensity recreational PA level of at least 3.9 h.week–1 in comparison to those achieving less than 1.4 h.week–1 (multivariable adjusted HR: 0.66; 95% CI, 0.48–0.91). Breast cancer mortality was also reduced by 46% in women reporting this level of PA in comparison to their more sedentary counterparts (multivariable adjusted HR: 0.56; 95% CI, 0.38–0.82). The results of this study suggest that habitual moderate intensity exercise which equates to current PA recommendations [13, 14, 26], if maintained throughout a woman’s lifetime, is sufficient to improve the chances of a positive outcome after diagnosis of breast cancer. Additionally, women who reported regularly engaging in >0.03 h.week–1 (i.e. >2 min.week–1) of vigorous intensity PA had a 26% reduced risk of breast cancer mortality in comparison to women reporting less than this (multivariable adjusted HR: 0.74; 95% CI, 0.56–0.98).

One further study investigated the association between pre-diagnosis PA levels and mortality in colorectal cancer patients. Non-occupational PA was assessed in 526 men and women aged 27–75 years (93% of the cohort were aged 40–69 years) who were enrolled onto the MCCS in Australia and later developed colorectal cancer [27]. At the baseline assessment, participants were asked (on average) how many
times per week during the last 6 months they engaged in vigorous, less vigorous and walking exercise before being classified as ‘exercisers’ or ‘non-exercisers’ and ‘walkers’ or ‘non-walkers’. During a median follow-up time of 5.5 years, there were 181 colorectal cancer deaths and 27 deaths due to other causes. Compared with no exercise, there were non-significant trends for a 23% improvement in overall survival (multivariable HR: 0.77; 95% CI, 0.58–1.03) and 27% improvement in colorectal cancer-specific survival (multivariable HR: 0.73; 95% CI, 0.54–1.00) for participants reporting any regular exercise (other than walking) in the 6 months prior to diagnosis. No association between walking exercise and colorectal cancer survival was apparent. Further analysis revealed a beneficial effect of exercise (versus no exercise) for patients with cancers that were stage II or III at diagnosis. In these patients, the risk of overall mortality within the follow-up period was reduced by more than a third (multivariable HR: 0.61; 95% CI, 0.41–0.92) and the risk of colorectal cancer-specific mortality was halved (multivariable HR: 0.49; 95% CI, 0.30–0.79). A better outcome in exercisers also appeared to be restricted to patients whose cancers originated in the right colon (multivariable HR: 0.50; 95% CI, 0.27–0.90). There was no association between PA and survival for rectal cancer.

Despite the relatively small sample sizes in some of these studies, they provide some evidence for the benefits of pre-diagnosis PA on outcome and survival after diagnosis of breast and colorectal cancer. Trends for an association between pre-diagnosis PA levels and breast cancer mortality were observed in older and younger breast cancer patients in two of the studies. A similar non-significant trend between pre-diagnosis PA and colorectal cancer mortality was also observed. Although pre-diagnosis PA might reflect post-diagnosis PA, there is evidence of a post-diagnosis decrease in PA levels compared to pre-diagnostic levels in breast and colorectal cancer patients [28, 29]. Alternatively, pre-diagnosis PA could influence disease progression and/or disease stage at diagnosis (or diagnosed tumours could be biologically less aggressive). However, evidence of stronger inverse associations in overweight breast cancer patients, stage II–III colorectal cancer patients and those with cancers originating in the right colon, does not support this. Further research with larger cohorts of breast, colorectal and other cancer survivors is warranted to substantiate these findings.

11.5 Post-diagnosis Physical Activity and Mortality in Breast and Colorectal Cancer Survivors

Recent studies have investigated post-diagnosis PA levels in breast and colorectal cancer survivors in relation to disease-free survival and mortality over a defined period of follow-up. These studies have yielded the most convincing observational evidence to date of the benefits to be gained from PA after a cancer diagnosis. Four recent studies of breast cancer survivors and two studies of colorectal cancer survivors have reported associations between post-diagnosis PA levels and mortality and an overview of the evidence from these studies will now be presented.
11.5.1 Breast Cancer Survivors

The first study to report an association between post-diagnosis PA levels and mortality in breast cancer survivors was published by Holmes et al. in 2005 [30]. In this study, PA data from the Nurses’ Health Study in the USA were examined in women diagnosed with stage I, II or III invasive breast cancer between 1984 and 1998. Beginning in 1986, leisure-time PA was assessed at least 2 years after diagnosis (median of 36 months post-diagnosis) to avoid the possibility of assessment during active treatment. Participants were asked to estimate the average time per week spent on a range of recreational activities, including walking, jogging, running, bicycling, swimming and sports activities, and the total MET-h.week\(^{-1}\) of leisure-time activity was determined. As walking was the most common form of PA undertaken by this cohort, the cut-points for leisure-time PA were chosen to correspond to different weekly durations of average-pace walking (2.0–2.9 mph). To determine the association between PA and breast cancer recurrence or mortality, women with a PA level equivalent to <1 h.week\(^{-1}\) of average-pace walking (reference category) were compared to women achieving higher levels of PA. Of the 2,987 women included in the analysis, 370 breast cancer recurrences and 463 deaths (280 breast cancer deaths) were recorded over a median follow-up time of 96 months.

Compared with the women who were least active, the risk of overall mortality during the follow-up period was reduced by 41% (multivariable RR: 0.59; 95% CI, 0.41–0.84) for women achieving the equivalent of 3–5 h.week\(^{-1}\) of average-pace walking. The risk of breast cancer recurrence was also reduced by 43% (multivariable RR: 0.57; 95% CI, 0.38–0.85) for women in this PA category, and the risk of breast cancer-specific mortality was reduced by 50% (multivariable RR: 0.50; 95% CI, 0.31–0.82). However, no further risk reductions (with respect to disease recurrence or breast cancer mortality) were observed for women performing higher levels of PA. Evidence that women with a higher stage of disease might engage in more PA compared with women diagnosed with in situ disease [31] might explain the plateauing of risk reduction at high levels of PA. A particularly interesting finding of this study was that obese women who are physically active can gain similar benefits from engaging in a physically active lifestyle as their slimmer counterparts. Overweight women with a BMI greater than 25 kg m\(^{-2}\) who were achieving the equivalent of 4–5 h of average-pace walking per week had a 56% risk reduction (multivariable RR: 0.44; 95% CI, 0.21–0.93) for breast cancer mortality in comparison to the least active overweight women in this BMI category. Furthermore, risk reductions in the range of 64–78% for breast cancer mortality were observed for obese women (BMI > 30 kg m\(^{-2}\)) achieving the equivalent of 4–6 h.week\(^{-1}\) of average-pace walking in comparison to the least active obese women. Further analysis based on a small number of deaths suggested that the beneficial effects of PA (equivalent to at least 3–5 h of average-pace walking) could be limited to women with hormone-receptor-positive tumours (consistent with a hormonal mechanism) and might be more pronounced in women with stage III disease (in comparison to stages I and II disease).
The findings of this study have since been consolidated by three other cohort studies of breast cancer survivors. Pierce et al. [32] assessed post-diagnosis PA levels in addition to vegetable–fruit intake in a cohort of 1,490 women from the Women’s Healthy Eating and Living (WHEL) Study. The women were all aged ≤70 years at diagnosis of early-stage breast cancer. All had completed primary therapy, although the majority were still taking tamoxifen. A 9-item questionnaire was used to record the frequency, duration and speed of walking outside the home, in addition to details of the frequency, intensity and duration of other physical exercise. Total energy expenditure for a given activity was expressed as MET-h.week⁻¹. Vegetable and fruit consumption was determined via a telephone-based dietary assessment (24-h dietary recall) on random days. Women were followed-up for an average of 6.7 years, during which time there were 118 breast cancer deaths and 17 deaths due to other causes.

In comparison to women with the lowest PA levels (average 3.7 MET-h.week⁻¹) and lowest vegetable–fruit consumption (average 3.1 servings.day⁻¹), women with the highest PA levels (mean of 25 MET-h.week⁻¹) who were consuming an average of 7.2 vegetable–fruit portions per day had a 44% reduced risk of mortality (multivariable HR: 0.56; 95% CI, 0.31–0.98). This level of PA equates to 4 h.week⁻¹ of brisk walking (6 METs) or 6–8 h.week⁻¹ of average-pace walking (3–4 METs). Further analysis revealed that the mortality rate for obese women in the highest PA and vegetable–fruit quartile was similar to that observed for normal weight women. In addition, higher PA and vegetable–fruit consumption appeared to confer greater survival advantages for women with hormone-responsive tumours. There was no evidence of risk reduction for women with high PA levels and low vegetable–fruit consumption or low PA levels and high vegetable–fruit consumption, and obese women in these latter two categories had an apparent increase in mortality compared to non-obese women.

Holick et al. [33] reported associations between post-diagnosis PA levels and mortality in breast cancer survivors from the CWLS, which is a population-based prospective cohort study investigating the contribution of modifiable lifestyle factors to longevity in women aged 20–79 years at breast cancer diagnosis. The women were mailed a questionnaire which was similar to that used in the Nurses’ Health Study [30] that assessed recreational PA within the last year a median of 5.6 years after breast cancer diagnosis. In addition, PA before diagnosis was available from a previous case–control study on the same cohort of women. The cohort comprised 4,482 women who were followed-up for a mean ± SD of 5.5 ± 1.1 years after returning the questionnaire. During this time, there were 109 breast cancer deaths and 303 deaths due to other causes.

Using the least active women as the reference, total recreational PA in the range of ≥2.8 to ≥21 MET-h.week⁻¹ was associated with risk reductions of 35–49% for breast cancer mortality (42–56% risk reductions for all-cause mortality). Further analysis revealed that only women who participated in moderate intensity PA had a lower risk of breast cancer mortality, whereas there was no association with vigorous PA. Furthermore, the benefits associated with moderate intensity PA were independent of the time interval since breast cancer diagnosis. Women who engaged in ≥2.0
to \( \geq 10.3 \text{MET-h.week}^{-1} \) of moderate intensity PA had 29–53% reduced risk of death from breast cancer (34–54% risk reductions for all-cause mortality) compared to women who engaged in \(<2 \text{MET-h.week}^{-1}\) of PA. A PA level of 10.5 MET-h.week\(^{-1}\) equates to a daily half-hour walk at average pace. There was a dose–response relationship for moderate intensity PA, such that an increment of 5 MET-h.week\(^{-1}\) was associated with 15% lower risk of breast cancer death (multivariable HR: 0.85; 95% CI, 0.74–0.98). Similar inverse associations between PA and breast cancer mortality were observed for young and older women at diagnosis, normal weight and overweight women and women diagnosed with local and regional stage disease.

In the most recent study, Irwin et al. [34] reported inverse associations between post-diagnosis PA and mortality in breast cancer survivors enrolled onto the HEAL Study, a multicentre, multiethnic prospective cohort study in the USA. All women had been diagnosed with \textit{in situ} to regional breast cancer and PA was assessed using in-person interviews. In this study, associations with both pre-diagnosis and post-diagnosis PA levels were investigated in samples of 933 and 688 breast cancer survivors, respectively. Pre-diagnosis PA was assessed a median of 5 months after diagnosis, and women were asked to recall their PA levels 1-year prior to diagnosis. Post-diagnosis PA levels were assessed during a follow-up interview conducted a median time of 2.5 years after diagnosis, in which women were asked to recall their PA levels during the last year. Information was collected on all types of PA but the main analysis was based on tertiles of sports/recreational PA. The impact of change in PA levels from pre- to post-diagnosis on risk of mortality was also investigated. During a median follow-up time of 6 years, there were 164 deaths (115 from breast cancer), 56 breast cancer recurrences and 40 new breast primary cancers.

A trend for a 31% risk reduction in total mortality was observed in women who were achieving the equivalent of 150 min.week\(^{-1}\) (30 min on at least 5 days of the week) of moderate intensity exercise in the year prior to breast cancer diagnosis (multivariable HR: 0.69; 95% CI, 0.45–1.06) in comparison to sedentary women. After diagnosis, any recreational PA and the equivalent of 150 min.week\(^{-1}\) of moderate intensity PA were associated with risk reductions of 64 and 67% (multivariable HR: 0.36; 95% CI, 0.17–0.73 and 0.33; 95% CI, 0.15–0.73), respectively. The benefits of PA appeared to be stronger for women diagnosed with higher stage disease (II–IIIA disease) and oestrogen-receptor-positive tumours but due to insufficient statistical power, these associations were not significant. There did not appear to be any association for women with oestrogen-receptor-negative tumours. Interestingly, women who decreased their PA levels by \(>3 \text{MET-h.week}^{-1}\) after the breast cancer diagnosis had a fourfold increased risk of death in comparison to inactive women (multivariable HR: 3.95; 95% CI, 1.45–10.50). No significant risk reduction for total mortality was observed in women who increased their PA levels by \(>3 \text{MET-h.week}^{-1}\) after being diagnosed with breast cancer.

Considered together, these studies show good evidence of an inverse association between post-diagnosis PA and mortality in breast cancer survivors. Three of the four cohort studies [30, 33, 34] show that women who are achieving the equivalent
of the recommended 30 min of moderate intensity PA on at least 5 days of the week [13, 14] can halve their risk of mortality in up to 8 years of follow-up. Whilst the benefits of PA appear to be equally applicable to overweight women, they were more pronounced in hormone-receptor-positive tumours and stage II–III disease in two studies [30, 32]. The levels of PA associated with risk reductions for mortality were higher in the WHEL cohort (equivalent to 6–8 h.week\(^{-1}\) of average-paced walking) but were only reported for women with high vegetable–fruit intake [32]. However, the benefits of lower PA levels were shown to be independent of vegetable–fruit consumption in the HEAL cohort [34]. A particular strength of the HEAL study is that it provided evidence of PA benefits in a multiethnic cohort, consistent with associations observed in the other cohort studies of mainly Caucasian women [30, 32, 33].

### 11.5.2 Colorectal Cancer Survivors

Recent evidence suggests that colorectal cancer patients can also benefit from PA following treatment. Meyerhardt et al. [35, 36] published two separate studies which showed an inverse association between post-diagnosis PA and mortality in colorectal cancer survivors. In the first of these studies, recreational PA levels were assessed in 832 patients enrolled on the CALGB adjuvant chemotherapy trial for stage III colon cancer [35]. These patients had undergone a complete curative-intent surgical resection of the primary tumour and had regional lymph node metastases (stage III) but no evidence of distant metastases. The PA assessment was undertaken approximately 6 months after completion of adjuvant chemotherapy (median of 7 months) to avoid the period of active treatment. Patients were asked to report the average time per week spent on various different recreational PAs, in addition to the number of flights of stairs climbed daily and their usual walking pace, from which total MET-h.week\(^{-1}\) of PA was calculated. Interim analysis showed that no difference in disease-free survival or overall survival would be observed from the different treatment arms (chemotherapy regimens) and so data were pooled and analysed according to PA levels. During a median follow-up time of 2.7 years, 159 patients had cancer recurrence and 84 patients died (with or without recurrent disease). Patients reporting 18–26.9 MET-h.week\(^{-1}\) of PA had a 49% improvement in disease-free survival (cancer recurrence or death from any cause) in comparison to the least active patients who engaged in less than 3 MET-h.week\(^{-1}\) (multivariable HR: 0.51; 95% CI, 0.26–0.97). Those achieving ≥27 MET-h.week\(^{-1}\) had a 45% improvement in disease-free survival (multivariable HR: 0.55; 95% CI, 0.33–0.91). Collapsing PA levels into two categories (<18 and ≥18 MET-h.week\(^{-1}\)) showed that patients who engaged in at least 18 MET-h.week\(^{-1}\) – the equivalent of walking 6 or more h.week\(^{-1}\) at average pace – had a 47% improvement in disease-free survival in comparison to patients engaging in <18 MET-h.week\(^{-1}\). The effect of PA appeared to be independent of sex, BMI, number of positive lymph nodes, age, baseline performance status or chemotherapy treatment arm.
In the second study, both pre- and post-diagnosis leisure-time PA levels were assessed in 573 women who had been treated with local or regional colorectal cancer (stages I–III) from the Nurses’ Health Study [36]. For the analysis of pre-diagnosis PA, responses from the survey immediately prior to diagnosis were used (median of 6 months before diagnosis). For the post-diagnosis analysis, the first PA assessment was collected at least 1 year but no more than 4 years post-diagnosis (median of 22 months after diagnosis) to avoid assessment during the period of active treatment. The women reported on a range of recreational activities, including walking, jogging, running, bicycling, swimming and sports activities. Each reported activity was assigned a MET score and the total MET-h.week\(^{-1}\) of leisure-time activity determined. During a median follow-up time since diagnosis of 9.6 years (with 95% observed for more than 5 years), there were 80 colorectal cancer-specific deaths and 52 deaths due to other causes. Patients reporting at least 18 MET-h.week\(^{-1}\) of recreational PA had a 61% improvement in colorectal cancer-specific mortality in comparison to the least active patients performing less than 3 MET-h.week\(^{-1}\) (multivariable HR: 0.39; 95% CI, 0.18–0.82). For overall mortality, an improvement of 57% was observed for patients engaged in this level of PA versus the least active patients. The inverse association between post-diagnosis PA level and colorectal cancer-specific mortality was not influenced by BMI, age, cancer stage or site of disease.

An additional feature of this study was the analysis of pre-diagnosis PA levels and the influence of a change in normal PA levels following diagnosis and treatment for colorectal cancer. The reported PA levels at a median of 6 months pre-diagnosis were not significantly associated with either colorectal cancer-specific or overall mortality. However, in contrast to the findings of Irwin et al. [34] for breast cancer patients, women in this study who increased their PA levels from pre- to post-diagnosis had a 52% improvement in colorectal cancer-specific mortality (multivariable HR: 0.48; 95% CI, 0.24–0.97) and a 49% improvement in overall mortality (multivariable HR: 0.51; 95% CI, 0.30–0.85) in comparison to women who did not change their PA level. Further analysis of the PA change data revealed similar benefits for women who increased their PA levels after treatment for colorectal cancer (irrespective of pre-diagnosis PA levels) and women who reported being consistently active throughout (for \(\geq 9\) MET-h.week\(^{-1}\)). In contrast, there was a non-significant increased risk for both colorectal cancer-specific and overall mortality in women who decreased their PA level from pre- to post-diagnosis.

These studies show that PA after a colorectal cancer diagnosis is associated with similar risk reductions for cancer-specific and overall mortality as those observed in physically active breast cancer survivors. In contrast to breast cancer patients, however, it seems that higher levels of PA than the current recommendations are needed in colorectal cancer survivors, i.e. the equivalent of 6 h of average-pace walking or 3 h of brisk walking per week (Fig. 11.1). There is evidence that the benefits of PA for colorectal cancer patients are similar for men and women of different body sizes and appear to be independent of cancer stage or site of the disease.
11.6 Does Physical Activity Have a Role in Prostate Cancer Mortality?

To date, no studies have investigated associations between pre- or post-diagnosis PA levels and mortality in men who have been diagnosed with PCa. However, evidence from primary prevention studies suggests that PA might provide some degree of mortality benefit through its impact on PCa progression. As it has been estimated that 15–30% of males over the age of 50 and as many as 80% over the age of 80 have undiagnosed PCa [37], lifestyle factors that can retard the progression of the disease could have a positive impact on mortality. Three large-scale prospective cohort studies have provided evidence of a strong inverse association between PA and incidence of advanced (or metastatic) PCa at diagnosis. This suggests that PA may have an important role to play in retarding PCa progression.

In the first of these studies, Giovannucci et al. [38] investigated PA levels in 47,620 men enrolled onto the Health Professional’s Follow-up Study in 1986, a prospective cohort study of US male health professionals aged 40–75 years. Men were asked to report the average time spent per week that they engaged in various recreational activities. From the questionnaire data, MET-h.week$^{-1}$ of total PA and vigorous or high-intensity PA were determined.
During the follow-up period to 1994, 1,362 total incident cases of PCa, 419 advanced (extraprostatic) and 200 metastatic cases were identified. Null relationships between PA and total and advanced PCa were observed for younger and older men. A 54% risk reduction for metastatic PCa was observed, however, for men achieving a median level of 5–7 h of vigorous PA per week in comparison to men not achieving any vigorous PA (multivariable RR: 0.46; 95% CI, 0.24–0.89). Further analysis showed a stronger inverse association between this level of vigorous PA and metastatic PCa risk in older men \( \geq 67.5 \) years of age (multivariable RR: 0.31; 95% CI, 0.10–0.99), indicating a 69% risk reduction. However, the equivalent of at least 3 h of vigorous PA per week appeared to confer some risk reduction for metastatic PCa in men of all ages. This risk reduction could be achieved through a variety of exercise modalities or a combination of several activities.

An extension of the 1998 study, but with follow-up to 2000 (14 years), allowed further refinement of the data analysis [39]. During follow-up, 2,892 incident cases of PCa were reported, including 482 advanced cases and 280 PCa deaths. Similar to the 1998 study, the authors observed no association between total PA level and total PCa, non-advanced, advanced or fatal PCa incidence, despite much improved statistical power from the 1998 report (approximately 600 cases per PA quintile). However, a strong negative association was again observed between vigorous PA and risk of advanced PCa in older men \( \geq 65 \) years of age). This report showed that a 67% risk reduction for advanced prostate (multivariable RR: 0.33; 95% CI, 0.17–0.62) could be achieved with 3–5 h of vigorous intensity PA per week in older men. Additionally, the Results for fatal PCa were similar to those observed for advanced PCa.

Another large-scale cohort study reported similar results for moderate intensity PA. Patel et al. [40] assessed recreational PA in 72,174 men aged 50–74 years (mean age of 64 years) who were enrolled onto the ACS Prevention Study II (CPS-II) Nutrition Cohort in 1992. At the baseline assessment, men were asked to quantify the amount of time spent doing various recreational activities during the past year and at the age of 40 years. Over 9 years of follow-up, 5,503 incident cases of fatal and non-fatal PCa were reported (4,160 cases of aggressive PCa and 1,343 cases of non-aggressive PCa). There was no association between level of recreational activity at baseline, at age 40 years or across multiple time-points during the follow-up period and risk of total PCa. However, the equivalent of 3.5–7 h of moderate intensity recreational PA per week was associated with a 23% risk reduction for aggressive PCa at diagnosis (multivariable RR: 0.77; 95% CI, 0.63–0.94) in men of all ages.

Lastly, a Norwegian prospective population-based study involving 29,110 men assessed PCa risk in relation to the average frequency, duration and intensity of recreational PA in a typical week [41]. During a median follow-up period of 17.5 years, 957 men were diagnosed with PCa, including 266 with metastatic disease at diagnosis and 354 men died from the disease. There was no association between frequency, duration or intensity of PA and overall risk of PCa. However, a statistically significant trend across frequency categories was observed for metastatic disease at
Exercise and Cancer Mortality

Men who were achieving at least one session of recreational PA per week had a 32% reduced risk of being diagnosed with metastatic PCa in comparison to men who were inactive (multivariable RR: 0.68; 95% CI, 0.46–1.02). A higher frequency of exercise sessions was associated with similar benefits, as was exercising (on average) for more than 1 h at each session (multivariable RR: 0.65; 95% CI, 0.42–1.00). This inverse association was consistent across age-groups, and there was evidence that higher PA summary scores (incorporating frequency, intensity and duration) were associated with lower risk. In addition, a 32% risk reduction for PCa mortality was observed for men who exercised on average for more than 1 h at each session (multivariable RR: 0.68; 95% CI, 0.47–0.98).

The results of these large-scale prospective cohort studies suggest that PA may have an important role to play in retarding the progression of PCa. Although there was some evidence that physically active men had healthier lifestyles and diet, the reported benefits of vigorous and moderate intensity PA did not appear to be influenced by more frequent PCa screening. Whether this translates into reduced risk of PCa mortality among physically active men is unknown but recent data from two large cohort studies does not support this [42, 43]. These studies found no association between PA levels in initially healthy men and future PCa mortality. Although Moore et al. [43] reported a 32% risk reduction for fatal PCa in the age-adjusted model (age-adjusted RR of 0.68; 95% CI, 0.52–0.89), this negative association was attenuated in the multivariable model. The authors felt that this was because physically active men are less likely to smoke or be overweight, factors which may each be associated with increased risk of fatal PCa.

Although the impact of habitual exercise on clinical end-points such as disease-free survival and mortality has not been investigated prospectively in PCa patients, a small-scale lifestyle intervention study of PCa patients yielded some promising preliminary evidence in relation to prognostic outcomes. In this study, Ornish et al. [44] investigated the effects of a combined low-fat diet and exercise programme on circulating PSA levels and treatment trends in men with early biopsy-proven PCa who had chosen not to undergo any conventional treatment (thus controlling for the confounding effects of treatment). The impact of the intervention on PCa cell growth in vitro was investigated by incubating baseline and post-intervention serum with the androgen-dependent PCa cell line LNCaP in cell culture. After 1 year, PSA had increased by 6% in the controls and decreased by 4% in intervention group. Body weight decreased by 4.5 kg in the intervention group and was unchanged in the controls. Six of the 49 control patients went on to conventional treatment (due to rising PSA) compared to none of the 44 patients in the intervention group. In the serum-stimulated LNCaP assay, cell growth was reduced by 9% in the controls and by 70% in the intervention group, but there was no difference between the groups in apoptosis or serum testosterone concentration. The authors stated that the intention was to follow-up the patients for a longer time period to establish the effect of the intervention on clinical end-points such as disease recurrence rates and mortality.
11.7 Physical Activity and Cardiovascular Mortality in Prostate Cancer Patients

Following a PCa diagnosis, PA might also have an important role to play in reducing the risk of CV mortality. ADT is being used increasingly in combination with local therapy to treat patients with high-risk localized PCa. However, there is evidence that ADT can lead to physiological changes that are characteristic of the metabolic syndrome, including increased circulating total cholesterol and triglyceride levels, body fat accumulation and insulin resistance [45–48]. This adverse metabolic profile for men receiving ADT is independent of age and BMI, suggesting a direct link with androgen deprivation [49].

Recent studies have also shown that PCa patients receiving ADT are at increased risk of serious CV morbidity and death from CV causes in comparison to similar men who did not receive ADT. PCa patients receiving ADT had a 20% increase risk of serious CV morbidity in comparison to men not receiving ADT after controlling for various factors, including pre-treatment cardiac disease (multivariable HR: 1.20; 95% CI, 1.15–1.26) [50]. Furthermore, patients treated with RP receiving ADT were more than twice as likely to die of CV causes over a median follow-up time of 3.8 years in comparison to patients not receiving ADT (adjusted HR: 2.6; 95% CI, 1.4–4.7) [51]. This increased risk of death from CV causes was evident in both younger (<65 years) and older (≥65 years) patients. A higher cumulative incidence of CV deaths was also observed in men treated with EBR therapy, BT or cryotherapy who received ADT but due to reduced statistical power, this did not reach statistical significance [51]. Given this evidence for an increased risk of CV mortality, there is a clear need to investigate the impact of PA interventions on CV risk profile and longer term clinical end-points such as CV mortality in PCa patients receiving ADT.

11.8 Summary and Conclusions

The weight of available observational evidence supports an inverse association between PA and mortality following a diagnosis of breast and colon cancer. Furthermore, evidence from primary prevention studies suggests that a physically active lifestyle might reduce the progression of PCa (but perhaps not overall occurrence of the disease). Although this might influence PCa mortality, there is currently no evidence to support this. It is important to note that the reported inverse associations between PA and mortality may only be applicable to cancer patients who survive the first several years after a cancer diagnosis. The duration of follow-up in cohort studies of cancer survivors was 3–10 years, and it is not known whether the apparent benefits of a physically active lifestyle extend beyond this. Additionally, misclassification of physical activity exposure should not be overlooked as the assessment methods which are typically used in observational studies of this type are susceptible to recall bias. In particular, post-diagnosis PA behaviour may have
in uenced the reporting of pre-diagnosis PA levels or PA could have been over-reported in an attempt to give a socially desirable response. There is evidence of a post-diagnosis decrease in PA levels compared to pre-diagnostic levels in breast and colorectal cancer patients [28, 29] and although levels may increase again after the period of active treatment, they may not return to pre-diagnosis levels [23, 29].

The possibility of ‘reverse causality’ is another important issue to consider in prospective cohort studies. In this context, the probability of reverse causality is increased if reduced PA levels are associated with worsening health in the immediate pre- or post-diagnosis period, when the PA assessments were undertaken in some studies. The most robust cohort studies of cancer survivors attempted to control for occult predictors of poor prognosis (such as the presence of sub-clinical disease) by excluding from the analysis any patients who died or suffered disease recurrence within a defined period of time (e.g. 24 months) after diagnosis or the PA assessment. Whilst this reduces the statistical power of the analysis, the inverse associations between PA and breast [33, 34] or colon cancer [35, 36] mortality continued to be evident.

A number different methods were used to grade PA, including average MET-h.week–1, MET-h.day–1, hours week–1, energy expenditure week–1 and frequency of sessions week–1 (or month–1). This can make it difficult to define the dose of PA (in terms of frequency, intensity, duration and modality) which is associated with optimum risk reductions for clinical outcomes such as cancer mortality. MET-h.week–1 takes into account estimates of intensity and duration but it is not possible to tease out the relative importance of exercise intensity unless separate analyses of moderate and vigorous intensity activities are included. In some studies, inverse associations with vigorous PA were stronger than for moderate intensity PA [15, 38, 39], and this is supported by a recent report which assessed associations between PA and all-cause mortality in cancer survivors using data from the Scottish Health Survey [52]. However, in other studies, stronger inverse associations between PA status and cancer mortality were observed for moderate intensity PA [30, 33] and associations with vigorous PA were either non-apparent [33] or positive [21]. Further research aimed at assessing the relative benefits of moderate intensity and vigorous exercise is clearly warranted.

The biological mechanisms which underpin the reported inverse associations between PA and cancer mortality have not yet been elucidated. The impact of PA on control of body weight or body fat levels and the in uence that this could have on putative risk factors for cancer, such as sex steroid hormones, IGF axis proteins, adipokines and inflammatory mediators, could be particularly important. However, the inverse associations between PA and cancer mortality in most of the cohort studies reviewed were consistent for both leaner and heavier participants, suggesting that the apparent benefit of a physically active lifestyle might not be mediated by effects on body weight or body fat. Other possible mechanisms, including improvements in the functioning of immune cells [53, 54], an increased antioxidant defence capacity [55] and exercise-induced alterations in gene function or apoptosis [56, 57], may account (to some degree) for the reported inverse associations.
In conclusion, a growing body of evidence supports the beneficial effects of PA in relation to cancer mortality, particularly in patients recovering from breast and colon cancer treatment. These observational studies need to be expanded into investigations of other cancer populations. In addition, RCTs are needed to provide more robust data on the frequency, intensity, duration and type of PA which could have the greatest impact upon disease-free survival in patients recovering from different forms of cancer and associated treatments.

References


Chapter 12
Ready to Change Lifestyle? The Feasibility of Exercise Interventions in Cancer Patients

Clare Stevinson

Abstract Cancer survivors generally have favourable attitudes and intentions regarding exercise, but the majority are not active at recommended levels. Studies suggest that less than a third of people with cancer are sufficiently active for general health maintenance. Interventions aimed at introducing participants to PA appear to be feasible, even for advanced cancer patients or those receiving intensive treatments. However, despite a focus on teaching behaviour change skills such as goal setting, self-monitoring, and reinforcement, most studies have not lead to sustained increases in PA behaviour. Cancer diagnosis is often described as a valuable ‘teachable moment’ regarding lifestyle changes, but for the majority of people with cancer, it appears that increasing habitual PA to levels appropriate for health promotion is a considerable challenge. Investigations of the barriers faced by cancer survivors in becoming more active suggest that the most common obstacles match those encountered by members of the general population (e.g. lack of time, motivation, energy), rather than being cancer-specific factors. Future developments in understanding how to improve exercise motivation and adherence among inactive individuals will therefore be useful for designing effective PA promotion strategies for cancer survivors.

12.1 Introduction

Historically, exercise was associated with healthy individuals and was perceived as incompatible with a diagnosis of cancer. However, as more effective treatments led to larger numbers of people surviving cancer, recognition grew of the importance of the right lifestyle choices for maximising health status and QoL. Although adequate rest is vital at the time of treatment and during recovery, an overemphasis on energy conservation can be problematic. Insufficient PA over time leads to frailty through
loss of physical conditioning and muscular strength, making it difficult to perform even basic activities of daily living. This was illustrated by a study comparing the physical performance limitations of 279 short-term (<5 years) and 434 long-term (≥5 years) cancer survivors with 9,370 individuals without a history of cancer [1]. Over half of the cancer survivors (54% short term and 53% long term) reported performance limitations versus 21% of the sample with no cancer history. The most common difficulties were crouching/kneeling, standing for 2 h, lifting/carrying 10 pounds, and walking quarter of a mile. Given that such actions are essential for simple activities of daily living (e.g. dressing, housework, childcare, shopping, gardening), the importance of PA for maintaining basic levels of physical performance is clear.

12.2 Physical Activity Recommendations

Since the value of remaining physically active after a diagnosis of cancer was first recognised [2], a growing body of research has accumulated indicating the range of benefits that can be achieved through exercise interventions. Results of meta-analyses suggest that in addition to increasing physical fitness and function, exercising during cancer treatment leads to fewer side-effects [3], while post-treatment exercise may result in small improvements in body composition, perceptions of fatigue, and QoL outcomes [3, 4]. Furthermore, observational studies have indicated that being physically active after a diagnosis of breast or colon cancer is associated with longer survival and reduced risk of recurrence [5–8]. This evidence has led to PA now being recommended to people diagnosed with cancer in several expert reports published by major cancer organisations [9–11]. These publications recommend that otherwise healthy cancer survivors aim for 30 min of moderate to vigorous intensity PA at least 5 times.week⁻¹ as part of a healthy lifestyle, to maximise QoL, and reduce risk of disease recurrence.

The impact of these recommendations has not yet been directly evaluated. Cancer diagnosis has been recognised as an important ‘teachable moment’ for initiating lifestyle changes [12]. However, the number of cancer patients who are provided with specific health promotion advice and the proportion who successfully implement such advice are difficult to determine. With regard to PA, survey data indicate high levels of interest and intention to exercise among people with cancer [13]. However, as with PA in the general population, actual participation levels are low. Samples of survivors of breast [14, 15], ovarian [16], endometrial [17], and bladder [18] cancer; multiple myeloma [19]; and non-Hodgkin lymphoma [20] suggest that only 20–30% report enough leisure-time PA to meet public health guidelines. For head and neck cancers the estimate is even lower at 9% [21]. In addition to the tumour site inhibiting many forms of PA, most participants in this study were at an advanced stage of disease. Conversely, brain tumour patients have slightly higher PA prevalence at 41% [22], which may reflect the relatively young age and high performance status of the study sample.
These data indicate that despite largely positive attitudes, adopting and maintaining a physically active lifestyle is a challenge for the majority of cancer survivors. This has led to the use of structured interventions that introduce individuals to regular exercise, with a view to them continuing to incorporate it as part of a healthy lifestyle. A great deal of research has focused on examining the feasibility of such interventions for people with cancer by providing information relating to adherence, tolerance, and acceptability.

12.3 Group Exercise

Several of these studies have employed group interventions, typically performed 2 or 3 times week\(^{-1}\). These have involved various forms of activity including circuit training, aerobics, aqua-aerobics, ball games, Tai Chi, dance, weight training, resistance bands, and aerobic fitness machines [23–37].

In general, adherence to these programmes was high with participation rates of 70–90\% [27, 30, 32, 37], even for those including patients on active treatment [28, 29, 34, 36]. Furthermore, no exercise-related adverse events were reported. Interventions proved highly popular with participants who provided positive feedback about the perceived benefits of the exercise and also the social support derived from the other group members. Because they exclusively consisted of people with cancer, the groups generated feelings of solidarity among participants who referred to a sense of comradeship like being ‘brothers in arms’ in the Army [27] or an ‘esprit de corps’ [38], and friendships with others who were in ‘a similar boat’ [37], and had ‘travelled the same road’ [31], or ‘fought your battle’ [32].

12.4 Home Exercise

Several other feasibility studies have used home-based exercise programmes typically involving walking [39–43], or other aerobic activities such as cycling, skating, skiing, and swimming [44, 45], performed 3–4 days week\(^{-1}\). Satisfactory compliance and tolerability were reported, with adherence to exercise programmes ranging from 52 to 75\%. Home-based programmes are convenient for participants but require greater self-motivation than supervised interventions and lack the social components of group sessions. One randomised trial compared self-directed home-based exercise with supervised gym-based exercise and usual care in a sample of 123 breast cancer patients. Although adherence was similar for the two approaches, improvements in physical functioning were actually greater with home-based exercise [46].

12.5 Long-Term Behaviour Change

Although the above studies are encouraging with regard to feasibility of exercise for cancer survivors, they generally have not included long-term follow-up to investigate if participants have maintained regular exercise beyond the intervention period.
For one study [35], assessments performed 1 and 3 months after the structured programme had ended indicated significant reductions in PA, although most participants were still exercising more than they had been prior to the intervention [47]. Meanwhile, other researchers have focused on interventions that build self-efficacy and behavioural skills in relation to PA, to help participants make lasting lifestyle change.

One of the most successful of these studies was a small randomised trial involving 45 obese endometrial cancer survivors [48]. The impact of a 6-month lifestyle intervention for changing dietary and PA behaviour was assessed in comparison with usual care (receiving an informational brochure). During the group-based intervention, participants were taught cognitive–behavioural techniques including goal setting, relapse prevention, and stress management. In addition, participants were given a pedometer to monitor PA and received newsletters and telephone calls to provide motivation and feedback. Results after 12 months indicated greater weight loss and higher frequency of PA among the intervention group.

A larger study examined the impact of a 6-month lifestyle PA programme on 134 men with PCa receiving continuous androgen ablation [49]. Participants were randomised to one of the three groups for 6 months: (1) lifestyle PA, (2) educational support, or (3) standard care. The lifestyle PA programme involved 90-min meetings in groups of eight participants, weekly for the first 16 weeks then bi-weekly for the last 8 weeks. The program taught cognitive–behavioural skills such as goal setting, self-monitoring, problem solving, and reinforcement focused on increasing daily PA with the aim of reaching 30 min of moderate intensity activity on most days of the week. The educational support programme was used to control for the group and facilitator effects. This involved facilitated discussions and expert speakers on topics such as treatment side-effects, diet, and sexuality, but included no skills training. A standard care group attended no meetings, but like the other groups received information about community resources.

Assessments at 6 months indicated that attendance at meetings was good, satisfaction was high, and no adverse events were reported. However, no differences between groups existed for self-reported PA or energy expenditure after 6 or 12 months. Similarly, the intervention had no effect on outcomes such as body composition, aerobic endurance, and QoL.

In a similar but smaller trial involving 60 breast cancer survivors, participants were randomised to either the lifestyle PA programme or the standard care [50]. At 6 months, endurance performance assessed by a 6-min walk test had improved more among the intervention participants than those receiving standard care, but strength tests were not different. Interestingly, motivational readiness for PA was greater among the intervention participants, but self-reported PA had increased for all participants and there were no differences between groups.

Another trial examined the effects of an exercise self-management programme on 34 older breast cancer survivors [51]. Participants were referred to the programme by oncologists and attended three weekly classes aimed at promoting exercise behaviour change. Classes introduced the basics of starting PA, taught cognitive–behavioural skills such as goal setting, contracting, and relapse prevention, and
covered other topics for promoting lifestyle change such as healthy attitudes, social support, and communication with doctors. Over the next 7 weeks, participants received three telephone calls to discuss progress and provide support. No control group was included in this study. Assessments at 6 months suggested small improvements in several measures of PA and energy expenditure, but significant increases only for leisurely paced walking.

The value of an exercise promotion booklet was assessed in a randomised trial involving 377 breast cancer survivors [52]. The booklet included information and guidance derived from research with breast cancer survivors based on the Theory of Planned Behaviour. Participants were randomly allocated to receive (1) the booklet, (2) a pedometer, (3) both the booklet and the pedometer, or (4) a standard recommendation to increase PA. Self-reported PA increased by nearly 90 min.week\(^{-1}\) in the two groups receiving the pedometer compared with the standard recommendation. Six months later, activity had decreased in all groups, and although the two groups with pedometers were still exercising over 50 min.week\(^{-1}\) more than at baseline, this was not significantly higher than the standard recommendation group (9 min more than baseline) [53].

The results of these studies illustrate the considerable challenge faced in attempting to make long-term changes to PA behaviour. Despite recruiting highly motivated participants, and designing interventions that teach behaviour change skills, there was generally little evidence of sustained increases in regular PA in these studies. This challenge is not unique to people with cancer, and PA promotion among the general population can be an equally difficult task. Considerable research has therefore been devoted to understanding the barriers faced by people in the attempt to become more active, and how these can be tackled.

### 12.6 Physical Activity Barriers

Studies of exercise behaviour among cancer survivors have identified a range of factors that inhibit PA in this population [54, 55]. Lack of time, energy, and motivation consistently prove to be the most commonly reported barriers, just as they are among the general population [56, 57]. Cancer-related barriers are reported relatively rarely. Even among patients still receiving adjuvant therapy for colorectal cancer, lack of time was reported more often than treatment-related side-effects as the reason for not exercising as planned [58]. In a survey of survivors of non-Hodgkin lymphoma, nausea and pain were each mentioned by 15% and peripheral neuropathy by 6% of respondents as factors that prevented them from being active, but lack of energy or physical strength was the major barrier (70%) [59].

Although lack of energy is a common perceived barrier across the general population, it is a particularly important obstacle for cancer survivors. Cancer-related fatigue is a prevalent symptom during treatment and often persists long term [60]. Interestingly, at the same time as citing lack of energy and fitness as barriers, cancer survivors typically identify reduced fatigue and increased fitness/strength as the
major benefits of exercise [59, 61]. These paradoxical beliefs reflect the inherent complexity of the fatigue/PA relationship. Although excessive activity may exacerbate fatigue, too much rest leads to physical deconditioning that contributes to increased fatigue during usual daily function. The aim is to achieve an appropriate level of PA that helps to prevent or reverse declines in fitness and function, without causing undue fatigue.

12.7 Advanced Cancer Patients

Exercise has also proved feasible for terminally ill or severely debilitated cancer patients. Two studies incorporated individualised exercise interventions within palliative care programmes for advanced cancer patients [62, 63]. The interventions involved walking, stretching, and resistance exercises, and were aimed at facilitating activities of daily living and providing symptom relief. Evaluation data from relatives and patients indicated high satisfaction and perceived benefits from the programmes. In another study, 63 patients with incurable cancer and short-life expectancy volunteered for a twice-weekly group exercise programme for 6 weeks [64]. Although 29 patients died or dropped out before the end of the programme, significant improvements in measures of fatigue and physical function were demonstrated among the 34 (53%) who completed the intervention. In a further interesting trial, 20 inpatients who had recently received bone marrow transplants underwent a supervised programme of treadmill walking [65]. A significant improvement in fitness measures was recorded within 6 weeks, reaching a performance level sufficient for carrying out activities of daily living. The authors observed that the typical spontaneous recovery of physical function in this population can take many months. These results indicate that PA should not only be promoted among patients with good prognoses or high performance status. Although there are relatively few studies with inpatients or palliative care patients, it is evident that in many cases exercise can be a realistic aim and can have meaningful benefits for these individuals.

12.8 Risks

When considering the feasibility of any intervention, it is important to assess the risk–benefit ratio. The risks associated with exercise at levels required for health promotion are low in the general population, and it is encouraging that few adverse events associated with exercise have been reported from trials with cancer survivors [3, 4, 66]. However, it should be noted that clinical trials have rigorous screening criteria and generally exclude participants for whom exercise may pose a potential risk. In the absence of any systematic data on safety, no definitive information exists regarding the risks associated with PA for people with cancer. For patients undergoing current or recent treatment, general concerns relate to the possibility of exercise leading to immunosuppression, falls, bone fractures, exacerbation of pain
and other symptoms, complications of cardiotoxic treatments, and interference with treatment completion or efficacy. Key precautions and suggested modifications to exercise interventions have been published to minimise risks [67].

A particular concern for breast cancer survivors who have undergone axillary node dissection is the risk of causing or exacerbating lymphedema through strenuous upper body exercise. The few studies that have addressed this concern have reported no increased risk associated with upper body resistance training or paddle training for dragon boat racing [31, 68–71]. Nonetheless, given the lack of evidence on this subject, the authors of a review of exercise and the lymphatic system concluded that continued caution was required by breast cancer survivors with and without a history of lymphedema when performing vigorous upper body exercise [72].

In assessing the risk–benefit ratio of exercise, it is important to consider the potential harm to cancer survivors of remaining inactive. Lack of PA leads to deconditioning, bone loss, and muscle atrophy; decreases in glucose metabolism, insulin sensitivity, digestive function and immunosurveillance; and increases in CV risk factors (e.g. lipid levels, blood pressure). Maintaining regular activity is essential, therefore, for reducing the risk of developing other chronic conditions (e.g. diabetes, CV disease, osteoporosis), and particularly so for cancer survivors who may at increased risk of other diseases [73, 74].

12.9 Summary and Conclusions

Cancer survivors generally have favourable attitudes and intentions regarding exercise, but the majority are not active at recommended levels. Interventions aimed at introducing participants to PA appear to be feasible, even for advanced cancer patients. However, despite a focus on teaching behaviour change skills, studies have not lead to sustained increases in PA behaviour. Although cancer diagnosis is perceived as a valuable ‘teachable moment’ regarding lifestyle changes, the challenge of increasing PA among cancer survivors to levels appropriate for health promotion is just as great as in the general population.

References


Chapter 13
Cardiorespiratory Exercise Testing in Adult Cancer Patients

Lee W. Jones

Abstract The use of exercise testing to provide an objective assessment of cardiorespiratory fitness in clinical oncology research has increased dramatically over the past decade. This chapter provides a comprehensive overview of the major recommendations for the specific performance of exercise testing in clinical oncology research. The adoption of consistent, standardized formal exercise testing methodology and data reporting standards are required to ensure high-quality exercise testing research in clinical oncology. Overall, information presented in this chapter provides critical information to clinicians and exercise oncology researchers who are conducting exercise testing among patients with cancer.

13.1 Introduction

Cardiorespiratory fitness is a recognized outcome of major importance in numerous clinical and research applications. Maximal or peak oxygen consumption (\(\dot{\text{VO}}_{2\text{peak}}\)) provides the gold standard measurement of cardiorespiratory fitness. \(\dot{\text{VO}}_{2\text{peak}}\) is determined by the product of cardiac output (Q) and arterio-venous oxygen difference (a-vO\(_2\text{diff}\)). The measurement of \(\dot{\text{VO}}_{2\text{peak}}\) is most commonly determined during an incremental CPET to exhaustion or symptom limitation. The measurement of \(\dot{\text{VO}}_{2\text{peak}}\) provides an objective measure of cardiorespiratory fitness, which varies considerably between individuals and is inversely correlated with CV and all-cause mortality among clinical and non-clinical populations [1–4]. Accordingly, formalized exercise testing is widely used in numerous clinical settings and provides a wealth of diagnostic, prognostic, and decision-making information [5].

The assessment of cardiorespiratory fitness, and thus use of exercise testing, is not part of the routine clinical management of cancer patients other than to determine the pre-operative physiologic status (i.e., operability) of patients with cancer.
pulmonary malignancies [6–13]. Over the past decade, however, the burgeoning interest in the role of exercise training interventions following a cancer diagnosis has led to a dramatic increase in the use of exercise testing to evaluate cardiorespiratory fitness [14–24]. In these investigations, exercise testing is performed before and after therapeutic interventions and can inform the development of individualized exercise prescriptions [14–24]. Unfortunately, a recent systematic review showed that the reporting of exercise testing methodology and data among adults with cancer, in general, does not comply with national and international quality guidelines [25]. Thus, the purpose of this chapter is to provide a comprehensive overview of the major recommendations for the specific performance of exercise testing in cancer patients. Formalized exercise testing guidelines have been issued by several national (e.g., American Thoracic Society/American College of Chest Physicians, ATS/ACCP) and international (e.g., European Respiratory Society, ERS) organizations, and the reader is referred to the ATS/ACCP recommendations for a comprehensive overview of exercise testing methodology for clinical populations [5].

13.2 Exercise Testing Methodology in Adult Cancer Patients

13.2.1 Pre-test Procedures

All oncology patients undergo a comprehensive medical and physical examination at diagnosis and prior to the initiation of therapy. As such, the attending oncologist is likely to have thorough knowledge of major potential exercise contraindications and obtaining oncologist approval for exercise testing should, in most circumstances, circumvent the need for other procedures (e.g., pulmonary function test, chest x-ray, etc.). On the day of testing, patients should be asked to abstain from behaviors (e.g., caffeinated beverages, smoking, exercise, etc.) that may alter heart rate, blood pressure, and arterial O2 saturation responses to exercise. The abstinence from medications that may alter these parameters is not required since exercise testing is not used for diagnostic purposes in the oncology setting.

13.2.2 Exercise Testing Modality

There are several methods available to investigators that enable the objective determination of cardiorespiratory fitness in adult cancer patients (Table 13.1). The first major consideration is whether to perform a maximal (with direct or estimated measurement of \( \dot{V}O_2\text{peak} \)) or submaximal exercise test. Maximal tests can be divided into two major categories: (1) direct measurement of \( \dot{V}O_2\text{peak} \) via incremental CPET with gas exchange measurement and (2) estimated measurement of \( \dot{V}O_2\text{peak} \) using standard formulas from the highest treadmill or cycle workload achieved. Both
| Table 13.1  Exercise test modalities |
|------------------|------------------|------------------|
| **Maximal**      | **Submaximal**   | **Constant Load test**^a^ |
| Direct measurement of VO₂ | Yes | No | No |
| Estimated measurement of VO₂ | No | Yes, estimated from highest workload achieved during the test | Yes, estimated from the workload achieved at a pre-defined HR (70-85% HRₘₐₓ) | No |
| Equipment         | • Expired gas measurement system • Electronically-braked cycle ergometer or motorized treadmill • 12-lead ECG • Pulse oximeter • BP monitoring | • Electronically-braked cycle ergometer or motorized treadmill • 12-lead ECG • Pulse oximeter • BP monitoring | • Electronically-braked cycle ergometer or motorized treadmill • 12-lead ECG • Pulse oximeter • BP monitoring | • 30 meter hallway/corridor • Heart rate monitor • Pulse oximeter • Stop watch |
| Cost              | Relatively expensive | Reasonable | Reasonable | Inexpensive | Inexpensive |
| Test Duration     | 8-12 minutes       | 8-20 minutes   | 8-20 minutes | 6 or 12 minutes | 5-30 minutes |
| Description of Test | Incremental exercise with expired gas analysis until volitional exhaustion or symptom-limitation | Incremental exercise until pre-defined HR (70-85% HRₘₐₓ) achieved | Subject asked to walk as far as possible in 6 or 12 minutes | Subject asked to pedal for as long as possible at pre-determined workload (50% to 70% workloadₘₐₓ) measured during incremental CPET |

^a^can only be performed following a CPET
Table 13.2  Criteria for an acceptable maximal exercise test

Acceptable test criteria for this assessment include any of the following:
- Peak or plateau in O$_2$ consumption concurrent with increased power output$^a$
- REP ≥ 1.15$^a$
- Predicted maximal work rate achieved
- Predicted maximal heart rate achieved
- Evidence of ventilatory limitation, i.e., peak exercise ventilation exceeds maximal ventilatory capacity (no evidence of a breathing reserve)
- Volitional exhaustion
- Symptom ratings 9–10 on the 0–10 scale

$^a$ applicable to CPET only

types of maximal tests are designed for the patient to achieve volitional exhaustion or symptom limitation (Table 13.2) and both provide accurate determination of cardiorespiratory fitness. Submaximal tests predict cardiorespiratory fitness based on the workload achieved at a given pre-determined submaximal heart rate. The decision to conduct maximal or submaximal exercise test should be determined by careful consideration of several factors including the purpose of the research investigation, the setting, and the patient population.

13.2.2.1 Purpose

Exercise testing is predominantly used for research applications in the oncology setting. In oncology clinical practice, exercise testing is used exclusively by thoracic surgeons and pulmonary physicians to measure pre-operative $\dot{V}O_2$peak in patients with pulmonary malignancies [6–13]. In this setting, clinicians have relied on CPET since it provides the most accurate assessment of $\dot{V}O_2$peak and risk of post-surgical complications [6–13]. At present, exercise testing is not currently used for any other indication and further research exploring the clinical value of exercise testing in the clinical management of oncology patients is warranted.

In oncology research applications, exercise testing has been used predominantly to provide (1) an objective determination of $\dot{V}O_2$peak or submaximal prediction of cardiorespiratory fitness and (2) exercise training prescription and cardiorespiratory fitness evaluation following therapeutic intervention in cancer patients. For both indications, use of CPET is recommended since it provides the most accurate assessment of cardiorespiratory fitness. It also provides a robust method of identifying asymptomatic CV abnormalities not permitted by resting pulmonary or cardiac function assessments which are commonly utilized in the oncology setting to assess whether cancer patients with certain types of malignancies qualify for certain types of cancer therapies and the effects (toxicity) of cancer therapy on cardiac and pulmonary function. The addition of CPET to these standard procedures may be useful for screening cancer patients prior to entry into behavioral (e.g., exercise) or pharmacologic (e.g., a new cancer agent that may cause CV abnormalities) intervention trials.
Despite the stark advantages of CPET, submaximal testing (without gas exchange measurement), which typically evaluates cardiorespiratory fitness in terms of time to the achievement of a pre-determined submaximal heart rate, may also be of value in oncology research applications. Such testing may be appropriate in frail or elderly cancer patients, when conducting a large number of tests in a nonclinic-based setting, or when appropriate medical supervision is not available. However, the investigator/clinician must be cautious when interpreting the results of such tests. Submaximal testing relies on an extrapolation of cardiorespiratory fitness from the work rate achieved at a given submaximal heart rate; thus, a significant potential for error exists because of the 10–20 beats.min⁻¹ standard deviation in maximal heart rate in normal subjects, as well as age-mediated errors in determining maximal heart rate [26]. There may be even greater variation in cancer patients who are experiencing autonomic dysfunction induced by pre-existing pathophysiology and further exacerbated by their current or previous systemic therapy or medications for other non-cancer-related disorders.

In addition to providing an evaluation of cardiorespiratory fitness, submaximal tests can also be used to assess functional capacity in terms of distance walked or time to fatigue in the oncology setting. For example, walk tests provide a simple, safe, and cheap objective assessment that can be performed in numerous clinical and research settings [27]; such tests have already shown utility in the oncology setting by several research groups [18, 24, 28]. Distance covered has been demonstrated to be a significant predictor of morbidity and mortality in a wide range of clinical populations [29–33]. These tests may provide prognostic information beyond that provided by subjective measures of functional capacity currently used in the oncology setting (i.e., performance status scoring systems). Of importance, however, functional test such as distance walked may not be sensitive enough to evaluate the effect on an intervention among patients with early-stage disease without significant underlying concomitant disease. Among these patients, a ‘ceiling effect’ may occur because such tests are unable to sufficiently stress patients to detect whether changes in cardiorespiratory fitness have transpired and maximal tests (with or without gas exchange measurement) are recommended.

### 13.2.2.2 Setting

Since CPETs are relatively expensive, require specialized personnel and equipment, and medical supervision, submaximal tests may be desirable in non-clinical settings. However, without physician supervision, even submaximal tests should only be conducted among cancer patients at ‘low risk’ (e.g., patients who have completed therapy for early-stage disease) of exercise-related adverse event. Submaximal tests may also be particularly useful for exercise promotion studies to provide complementary, objective data on change in cardiorespiratory fitness or functional capacity associated with change in exercise behavior (assessed by self-report or other tools). However, clinical-based studies should strive to conduct CPET wherever possible, especially given the wealth of clinical information that can be obtained from such tests.
13.2.2.3 Patient Population

In general terms, a CPET is the logical choice for the majority of cancer patients who typically are older and commonly present with concomitant comorbid disease that may limit exercise tolerance [21–23]. Furthermore, oncology patients receive a broad range of locoregional (e.g., surgery, radiation) and systemic (e.g., chemotherapy, targeted biologic therapy) therapies that may simultaneously adversely affect several steps in O₂ transport (i.e., pulmonary diffusion capacity, CV O₂ delivery, and oxidative phosphorylation) [34]. For example, pulmonary resection is associated with a 12–20% reduction in ŔVO₂peak [12, 24, 35]. Additionally, anti-cancer therapies (i.e., radiation, chemotherapy, targeted biologic therapy) as well as symptom control medications (e.g., glucocorticoids) cause cardiac perfusion defects [36], overt and subclinical declines in left ventricular ejection fraction [37], anemia [38], autonomic dysfunction [39, 40], pulmonary fibrosis [41, 42], peripheral vascular endothelial dysfunction [22, 43], and skeletal myopathy [44, 45].

As such, a CPET is recommended since it provides the most accurate determination of ŔVO₂peak and can identify the underlying mechanism(s) of limitation. The utility of the CPET for determination of ŔVO₂peak has been demonstrated in the oncology setting by several research groups [9, 17, 22, 46]. However, the relative importance of factors that contribute to exercise limitation in cancer patients has not been examined [47]. Finally, the prognostic value of ŔVO₂peak on cancer-specific and all-cause mortality following diagnosis is not known.

Certain cancer diagnoses are associated with tumor-induced (e.g., lung, colorectal, pancreas) and steroid-induced (e.g., primary glioma, brain metastases) cachexia or severe peripheral muscle weakness. The presence of skeletal myopathy can lead patients to terminate exercise before adequate or meaningful measures of the exercise response can be assessed due to localized leg fatigue [48]. This is particularly problematic during cycle ergometer-based CPET protocols. In these situations, constant load tests that require patients to exercise at 65–90% of maximal exercise capacity until symptom limitation are more appropriate for assessing submaximal cardiorespiratory fitness. These tests are also useful for evaluating the efficacy of therapeutic interventions in other clinical populations that experience disease and/or treatment-associated skeletal myopathy (e.g., heart failure, COPD) [49–51].

13.2.3 Exercise Testing Safety

To date, formal, large-scale evaluations of the safety of exercise testing in the oncology setting have not been conducted. Results of a recent systematic review suggest that maximal and submaximal exercise testing is a relatively safe procedure, with adverse events being reported in <15% of all studies and with no reported exercise test-related deaths. However, less than half have employed maximal CPET procedures and even fewer have conducted physician-monitored, ECG protocols. As such, it is not clear whether the low incidence of events reflects the true safety or less than optimal exercise test methodology and/or data reporting. The ATS/ACCP report that the risk of death and life-threatening complications during exercise testing is 2–5
per 100,000 tests [5]. Maximal, particularly submaximal, exercise testing is a relatively safe procedure, especially in patients without significant underlying disease. Nevertheless, given that the effects of cancer and cancer therapy on pathophysiologic mechanisms of exercise tolerance are not known and a high proportion of cancer patients have significant concomitant comorbid disease, the risk of an exercise test-related event may be elevated. Thus, appropriate screening and testing procedures are mandated [25]. The reporting of whether adverse events did or did not occur is also mandatory for all exercise oncology studies. The safety of exercise testing ultimately depends on two critical factors: (1) eligibility criteria/patient selection and (2) exercise test conduct/methodology.

### 13.2.3.1 Eligibility Criteria

We believe that the ATS/ACCP absolute and relative contraindications are appropriate for exercise testing in cancer patients, with modification to include presence of extensive skeletal and visceral metastases and untreated anemia (Table 13.3). To

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction (3–5 days)</td>
<td>Left main coronary stenosis or its equivalent</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>Moderate stenotic valvular heart disease</td>
</tr>
<tr>
<td>Uncontrolled arrhythmias causing symptoms or hemodynamic compromise</td>
<td>Severe untreated arterial hypertension at rest (&lt;200 mgHg systolic, &gt;120 mmHg diastolic)</td>
</tr>
<tr>
<td>Syncope</td>
<td>Tachyarrhythmias or bradyarrhythmias</td>
</tr>
<tr>
<td>Active endocarditis</td>
<td>High-degree atrioventricular block</td>
</tr>
<tr>
<td>Acute myocarditis or pericarditis</td>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Symptomatic severe aortic stenosis</td>
<td>Significant pulmonary hypertension</td>
</tr>
<tr>
<td>Uncontrolled heart failure</td>
<td>Advanced or complicated pregnancy</td>
</tr>
<tr>
<td>Acute pulmonary embolus or pulmonary infarction</td>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td>Thrombosis of lower extremities</td>
<td>Orthopedic impairment that compromises exercise performance</td>
</tr>
<tr>
<td>Suspected dissecting aneurysm</td>
<td>Untreated anemia (Hb level between 80 and 110 g.L$^{-1}$)</td>
</tr>
<tr>
<td>Uncontrolled asthma</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td></td>
</tr>
<tr>
<td>Room air desaturation at rest ≤85%</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td></td>
</tr>
<tr>
<td>Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e., infection, renal failure, thyrotoxicosis)</td>
<td></td>
</tr>
<tr>
<td>Mental impairment leading to inability to cooperate</td>
<td></td>
</tr>
<tr>
<td>Evidence of extensive visceral and/or skeletal metastases</td>
<td></td>
</tr>
</tbody>
</table>
optimize patient safety, prior to exercise testing all patients should undergo a clinical status examination. The examination should include clinical diagnosis, stage of disease, prior or current treatments, PA profile, appropriate laboratory tests (e.g., Hb [80–110 mg.dL\(^{-1}\]), complete blood counts, etc.), resting ECG, determination of exercise contraindications, and oncologist/physician approval. Most of these examinations are performed in routine oncology visits and/or can be abstracted from the patient’s medical chart. PA profile will inform the clinician/investigator of the most appropriate type of exercise test (maximal versus submaximal), modality (cycle ergometer versus treadmill), protocol (set versus individualized intensities) to be used. The oncologist/physician can screen potentially eligible patients for exercise test contraindications during routine clinical evaluations. In non-clinical settings, patients must receive physician clearance or complete a pre-exercise screening questionnaire (e.g., PARmed-X [52]) prior to exercise testing.

### 13.2.3.2 Exercise Test Conduct/Methodology

The principal considerations are (1) exercise equipment, (2) exercise test protocol, and (3) monitoring of patient exercise response.

**Exercise equipment**: The two types of exercise equipment for the majority of cancer patients are treadmill and cycle ergometer. Motor-driven treadmills provide progressively increasing exercise intensity through a combination of speed and grade (elevation) according to the selected protocol. Treadmill-based exercise tests are attractive, as walking is a more natural and familiar activity than cycling for most cancer patients. The main disadvantages of treadmill exercise tests are the difficulty of quantifying external work rate and the coordination/balance requirements. The latter point is an important consideration in older cancer patients and those suffering from treatment-associated ataxia or peripheral neuropathy. Coordination/balance difficulties may alter the heart rate and blood pressure responses to exercise.

In contrast, cycle ergometer exercise tests are advantageous for cancer patients for the following reasons: (1) less prone to introduce movement and noise artifact into exercise response measures, (2) require less coordination and balance than treadmill walking, and (3) work rate is quantifiable. For most clinical situations in the oncology setting, cycle ergometry is recommended. Irrespective of which exercise mode is selected, it must be kept consistent when conducting serial assessments because \(\dot{V}O_2\text{peak}\) has been reported to be 5–10% higher on a treadmill than a cycle ergometer [53].

**Exercise Test Protocol**: To assess cardiorespiratory fitness within a timely and standardized manner, there are several maximal incremental, ramp protocols available. These protocols can be used with either a cycle ergometer or treadmill and are classified according to the application of work rate: (1) constant increments (application of same workload increments for all patients) or (2) individualized increments (variable workload increments based on patient characteristics). Individualized
incremental protocols enable the selection of patient-appropriate workload increments; this degree of flexibility is especially useful when conducting CPETs in cancer populations presenting with a varying levels of concomitant comorbidities and treatment history. Standardization of exercise test methodology is required in order to maximize the reproducibility of such tests which is critical when conducting repeated measures and/or assessing the efficacy on therapeutic interventions. Serial testing should also be conducted on the same exercise equipment, at the same time of the day, and preferably, by the same study personnel.

Finally, a component of CPET methodology that is of the utmost importance, as it determines both the reliability and validity of obtained data, is pre-CPET equipment calibration and quality control. On the day of exercise testing, a pre-test equipment calibration should be conducted according to the manufacturer’s guidelines to ensure quality control. A post-test equipment calibration check is also recommended to confirm data quality. This is important if a number of exercise tests are being conducted on the same piece of exercise equipment with different personnel and cancer patient populations.

**Monitoring of Patient Exercise Response:** Heart rate, blood pressure, pulse oximetry, and 12-lead ECG monitoring are recommended for all cancer patients prior to, during, and following exercise testing. The level of physiologic monitoring should be determined by the type of exercise test selected (maximal versus submaximal). For Example, 12-lead ECG and physician monitoring are not required when conducting submaximal exercise tests in asymptomatic cancer patients exercising within their habitual exercise levels. However, such monitoring is mandatory when conducting maximal tests (e.g., CPET). A recent systematic review found that, with the exception of heart rate monitoring in CPET studies, up to two-thirds of oncology studies did not monitor key exercise outcomes prior to or during exercise testing [25]. Inclusion of these assessments permits early detection of exercise-associated abnormalities/complications for test termination and provides detailed information on patient response to different exercise intensities. This information can supplement $\dot{V}O_2$peak data enabling the design and implementation of optimal and safer exercise prescriptions. Particularly useful is the determination of ventilatory threshold from the CPET data. Ventilatory threshold is defined as the point during graded exercise in which ventilation increases disproportionately to $O_2$ uptake. Identifying the ventilatory threshold can aid in the optimization of exercise prescription and may be more sensitive to change following an exercise intervention than $\dot{V}O_2$peak.

Submaximal exercise responses during the incremental CPET test can also provide valuable data that can help identify potential mechanisms of exercise limitation and assist with the individualization of exercise prescriptions in cancer patients. For example, the $V_\dot{O}_2$–external work rate relationship provides important information regarding the efficiency of movement, inadequacies in $O_2$ delivery, and potential skeletal muscle dysfunction. In addition, heart rate and $O_2$ pulse (capacity of the heart to deliver $O_2$ per beat) supply further important information on the cardiopulmonary response to physiologic stress (e.g., exercise).
13.3 Exercise Test Results Reporting

Formal guidelines on exercise test data reporting do not currently exist for any clinical population including cancer patients. A considerable number of variables can be non-invasively measured and derived from all types of exercise tests (Table 13.4). However, the reporting of certain key measurements is critical to accurately evaluate the quality and implications of the research in oncology research studies and practice. The ATS/ACCP suggests reporting resting pulmonary function data for all patients. However, in the oncology setting, these data may only be required for patients with primary lung cancer, lung metastases, those receiving thoracic RT, or undergoing systemic therapy associated with pulmonary dysfunction (i.e., gemcitabine) [54]. The importance of reporting of certain outcomes cannot be understated. For example, without reporting peak heart rate or RER data, it is not known whether a maximal CPET was conducted or whether the exercise test data are valid. The reporting of ventilatory parameters (e.g., minute ventilation, tidal volume, and respiratory frequency) is also important, particularly in patients with lung malignancies or respiratory comorbidities and it advanced cancer patients with pulmonary metastases. Finally, the reporting of normal reference values provides the comparative basis from which the normalcy of the exercise responses can be interpreted. Normal reference values for maximal and submaximal tests are available for both a wide range of cardiopulmonary and pulmonary gas exchange variables. When choosing appropriate reference values, each exercise laboratory should choose normative data obtained from individuals with similar characteristics to the cancer population tested. Appropriate normative data for peak heart rate and $\dot{V}O_2_{peak}$ are provided by Fitzgerald et al. [55] (women) and Wilson and Tanaka (men) [56].

<table>
<thead>
<tr>
<th>Table 13.4</th>
<th>ATS/ACCP exercise testing data reporting recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>$SpO_2_{rest}$</td>
<td>$SpO_2_{peak}$</td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>AT</td>
</tr>
<tr>
<td>$O_2$ pulse</td>
<td>Workload</td>
</tr>
<tr>
<td>RER</td>
<td>Ventilatory parameters</td>
</tr>
<tr>
<td>Symptoms/RPE</td>
<td>Comparison with reference normative values</td>
</tr>
<tr>
<td>Predicted oxygen consumption</td>
<td>Adverse event reported</td>
</tr>
</tbody>
</table>

Abbreviations: $SpO_2$, arterial oxygen saturation; AT, anaerobic threshold; RER, respiratory exchange ratio; RPE, rate of perceived exertion
In other non-cancer clinical populations, the quantification and characterization of symptoms during exercise or following therapeutic intervention are increasingly being reported because of the relationship with physiologic variables [57, 58]. In addition, many patients with chronic disease, including those with cancer, are symptom limited; thus, assessment of these variables is both of clinical and practical importance. Finally, knowledge of patient effort, as well as reason for test termination, is important when determining the extent and cause of exercise limitation. The most commonly evaluated symptoms are exertional dyspnea and leg discomfort measured using the modified Borg scale [59].

### 13.4 Summary and Conclusions

While the clinical application of exercise testing in cancer management outside of the pre-operative lung setting remains to be determined, the rapid development of exercise oncology research suggests that the application of exercise testing is only likely to increase in the forthcoming years. To this end, exercise oncology research laboratories should adopt existing standardized guidelines for the performance of exercise tests, as issued by several national (e.g., ATS/ACCP) and international (e.g., ERS) organizations. The adoption of such guidelines is critical to ensure high-quality exercise testing research in clinical oncology.

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