

**Exercise, Functional Capacity and  
Quality of Life in Peripheral Blood Stem Cell  
Transplant Patients**

**Sandra C Hayes**

Bachelor of Applied Science (Human Movement Studies)  
First Class Honours Division A

**Queensland University of Technology**  
Faculty of Health  
School of Human Movement Studies

**Thesis submitted for the degree of Doctor of Philosophy**

**2001**



QUEENSLAND UNIVERSITY OF TECHNOLOGY  
DOCTOR OF PHILOSOPHY THESIS EXAMINATION

CANDIDATE NAME: *Sandra Christine Hayes*  
RESEARCH CONCENTRATION: *Physical Activity and Disability*  
PRINCIPAL SUPERVISOR: *Associate Professor Peter Davies*  
ASSOCIATE SUPERVISOR: *Professor Tony Parker*  
THESIS TITLE: *Exercise, Functional Capacity and Quality of Life in Cancer*

*Under the requirements of PhD regulation 16.8, the above candidate presented a Final Seminar that was open to the public. A Faculty Panel of three academics attended and reported on the readiness of the thesis for external examination. The members of the panel recommended that the thesis be forwarded to the appointed Committee for examination.*

Name: *Associate Professor Peter Davies*  
*Panel Chairperson (Principal Supervisor)*

Name: *Professor Tony Parker*  
*Panel Member*

Name: *Professor Beth Newman*  
*Panel Member*

*Under the requirements of PhD regulations, Section 16, it is hereby certified that the thesis of the above-named candidate has been examined. I recommend on behalf of the Examination Committee that the thesis be accepted in fulfillment of the conditions for the award of the degree of Doctor of Philosophy.*

Name: *ANDREW HILLS*  
*Chair of Examiners (Head of School or nominee) (Examination Committee)* Date: *10/09/01*

## Key Words

---

Aerobic capacity, aerobic exercise, body composition, bone marrow transplant, bone turnover, cancer, cancer rehabilitation, energy expenditure, exercise, functional capacity, immunology, intervention, muscular strength, oncology, peripheral blood stem cell transplant, physical activity, quality of life, recovery, resistance training, side effects, treatment.

## Abstract

---

As medical technology has advanced, outcomes have improved for many malignancies, and thus survival rates for those diagnosed with cancer are progressively increasing each year. However, as a consequence of the disease process and cancer treatment, patients commonly experience adverse physiological and psychological changes. Determining the impact of these side effects on functional capacity and quality of life (QoL), as well as investigating intervention strategies that maintain the ability to facilitate recovery post-treatment, is essential for the cancer patient, as survival rates continue to rise.

Twelve patients undertaking an intensive treatment regime of high-dose chemotherapy, followed by peripheral blood stem cell transplantation were recruited into this investigation. The study participants were aged between 16 to 64 years and had been diagnosed with either advanced breast cancer, leukaemia, lymphoma, multiple myeloma or rhabdomyosarcoma. Functional capacity and quality of life were assessed pre-transplant (Phase I - PI), post-transplant (Phase II - PII) and following a 12-week intervention period (Phase III - PIII). Functional capacity measures included body composition, energy expenditure, aerobic capacity, muscular strength, immunological status and function and bone turnover. Pre- and post-transplant measures demonstrated that undertaking a transplant was associated with adverse changes to body composition, muscular strength, aerobic fitness, immunological status, and bone turnover, which together maintain the potential to influence functional capacity in the short- and longer-term. The treatment regime was also associated with adverse changes in total QoL.

Participation in regular physical activity has been linked with numerous physiological and psychological benefits in healthy and certain diseased populations. However, the potential benefits derived through participation in exercise are less clear for patients with cancer. This investigation was designed to extend current evidence regarding exercise, functional capacity and QoL in peripheral blood stem cell transplant patients, and therefore post-treatment, the study group was divided equally into a control group (CG) or exercise intervention group (EG). The exercise

intervention protocol was of a moderate intensity and mixed type nature. Exercising patients participated in aerobic exercise three times per week, for 20-40 minutes at an intensity of 70-90% of their maximum heart rate. Additionally, resistance training, which involved the performance of one set, 8-20 repetitions of 3-6 machine and free weight exercises, was scheduled twice per week.

Patients in the exercise group demonstrated a faster recovery of lean tissue ( $p<0.01$ ), aerobic capacity ( $p<0.05$ ), muscular strength ( $p<0.05$ ) and QoL ( $p<0.05$ ) when compared with the non-exercising patients. Additionally, by 3-months post-transplant, exercising patients were experiencing higher peak ventilation ( $p<0.05$ ), lower body strength ( $p<0.01$ ) and QoL ( $p<0.05$ ), when compared with the controls, and were demonstrating comparable aerobic capacity to healthy age-matched controls. Patients had improved body composition, aerobic capacity, peak ventilation and body strength at PIII, when compared with pre-transplant measures ( $p<0.05$ ). Correlations performed on QoL data with aerobic capacity data indicated that those who were experiencing a higher level of fitness were more likely to also experience a higher QoL ( $R=-0.685$ ;  $p<0.05$ ), and fewer ( $R=-0.630$ ;  $p<0.05$ ) and less severe ( $R=-0.708$ ;  $p<0.01$ ) QoL problems.

Following the intervention period, the bone turnover changes observed in the exercise participants indicated an uncoupling of formation and resorption activity, favouring formation. The control group failed to demonstrate these changes during the same period, and although preliminary, collectively the results suggest that participation in the intervention protocol may have a favourable influence on bone metabolism. In contrast to the other functional capacity measures, participation in the exercise intervention had no impact on immunological changes across the testing phases as was evident by both exercising and non-exercising patients demonstrating a delayed recovery for lymphocyte, CD3+, and CD4+ cell counts. Importantly though, while exercise did not facilitate the recovery of these immune cells, immune recovery was not adversely effected, demonstrating that participation in the prescribed exercise program was of no detriment to immune status and function for these patients.

In summary, participation in exercise following cancer treatment facilitates the recovery of numerous physiological variables, which in turn influences functional capacity and QoL. Additionally, patients maintain the capacity to return to higher than pre-transplant functional capacity and QoL, in as little as three months following treatment. This investigation not only highlights the need to integrate exercise into the care plan of patients with cancer following treatment, but also provides evidence demonstrating that participation in an exercise program can assist in 'bridging the gap' between treatment cessation, and returning to a 'normal' lifestyle.

## Table of Contents

---

<b>Key Words</b>	<b>ii</b>
<b>Abstract</b>	<b>iii</b>
<b>Table of Contents</b>	<b>vi</b>
<b>List of Figures</b>	<b>xi</b>
<b>List of Tables</b>	<b>xv</b>
<b>List of Abbreviations</b>	<b>xvii</b>
<b>Statement of Original Authorship</b>	<b>xviii</b>
<b>Abstracts Arising from Thesis</b>	<b>xix</b>
<b>List of Acknowledgements</b>	<b>xx</b>
<b>Chapter One: Introduction</b>	<b>1</b>
1.0 Introduction	2
1.0.1 Physical activity participation rates	3
1.1 Cancer	4
1.1.1 Cancer incidence and mortality rates	4
1.2 Exercise and cancer prevention	5
1.2.1 Mechanisms by which exercise may influence the presence/ absence of cancer	7
1.3 Cancer treatment	9
1.3.1 Bone marrow transplantation and peripheral blood stem cell transplantation	11
1.4 Cancer rehabilitation	16
1.4.1 Exercise as a component in cancer rehabilitation	19
1.4.2 Lack of referral	20
1.5 General research purpose	22
<b>Chapter Two: General Literature Review</b>	<b>26</b>
2.0 Introduction	27
2.1 Exercise prescription for cancer patients	28
2.1.1 Exercise variables	28
Type	28
(a) Aerobic Exercise	29
(b) Resistance Training	32
(c) Mobility Exercise	35
2.1.2 Considerations during exercise prescription	35

**Chapter Three: Study Design and General Methodology 38**

3.1	Study design	39
3.2	Patient type	40
3.3	Ethical approval of research	40
3.4	Determination of sample size and recruitment of subjects	41
3.5	Autologous peripheral blood stem cell transplant procedure	42
3.6	Exclusion criteria	43
3.7	Recruitment of subjects into experimental groups	44
3.8	Testing phases	46
3.9	Experimental groups	48
3.9.1	The intervention program	48
3.10	Statistical analysis of data	52

**Chapter Four: Study One**

**Changes in energy expenditure and body composition following a PBST and participation in an exercise program 55**

	List of abbreviations specific to Chapter four	56
4.0	Introduction	57
4.0.1	Purpose	58
4.1	Literature Review	59
4.1.1	Total energy expenditure	59
4.1.1.1	Resting energy expenditure	61
4.1.1.2	Energy intake and thermogenesis of food	62
4.1.1.3	Physical activity	64
4.1.2	Impact of cancer treatment on body weight and body composition	65
4.1.3	Impact of exercise on body weight and body composition	70
4.1.4	Use of body composition assessment methods	73
4.2	Methodology	75
4.2.1	Height, weight and body mass index	75
4.2.2	Body composition	75
4.2.2.1	Singly labelled water technique	75
4.2.2.2	Skinfold technique	78
4.2.3	Energy expenditure – doubly labelled water technique	78
4.2.4	Dietary assessment	80
4.2.5	Statistical analysis	81
4.3	Results	83
4.4	Discussion	93
4.4.1	Body composition and total energy expenditure	93
4.4.2	Limitations of research and directions for future research	99
4.5	Conclusion	101

**Chapter Five: Study Two**  
**Changes in aerobic capacity and muscular strength following a PBST and participation in an exercise program** 102

List of abbreviations specific to Chapter five	103
5.0 Introduction	104
5.0.1 Purpose	105
5.1 Literature Review	106
5.1.1 Physical status of cancer patients	109
5.1.2 Fatigue	111
5.1.3 Aerobic exercise and cancer patients	112
5.1.3.1 Aerobic exercise studies	112
5.1.4 Strength training and cancer patients	115
5.1.4.1 Strength training studies	116
5.2 Methodology	118
5.2.1 Cardiorespiratory assessment	118
5.2.2 Muscular strength assessment	121
5.2.3 Statistical analysis	121
5.3 Results	123
5.4 Discussion	130
5.4.1 Testing procedures and expression of results	130
5.4.2 Pre-transplant function	132
5.4.3 Post-transplant function	132
5.4.4 The importance of a physical intervention program	134
5.4.5 Longer-term implications of PBST or BMT	140
5.5 Conclusion	141

**Chapter Six: Study Three**  
**Changes in immunological status and function following a PBST and participation in an exercise program** 142

List of abbreviations specific to Chapter six	143
6.0 Introduction	144
6.0.1 Purpose	145
6.1 Literature Review	146
6.1.1 Immune system status	148
6.1.2 Immune system status of patients with cancer	151
6.1.3 Exercise and the immune system	154
6.1.4 Exercise, cancer and the immune system	160
6.1.5 Exercise, HIV and the immune system	163
6.2 Methodology	166
6.2.1 T cell number and function	166
6.2.2 Statistical analysis	170
6.3 Results	171

6.4	Discussion	178
6.4.1	Pre-transplant immune parameters	178
6.4.2	The impact of a PBST on T cell number and function	180
6.4.3	Changes in immune parameters post-transplant	181
6.4.4	The role of exercise in immune system recovery	185
6.5	Conclusion	187

## **Chapter Seven: Study Four**

### **Changes in bone turnover following a PBST and participation in an exercise program 188**

	List of abbreviations specific to Chapter seven	189
7.0	Introduction	190
7.0.1	Purpose	191
7.1	Literature Review	192
7.1.1	Assessment of skeletal status	192
7.1.2	Factors influencing skeletal status and risk of osteoporosis	194
7.1.2.1	Disease- and drug-related bone loss	194
7.1.2.2	Dietary-related bone loss	200
7.1.2.3	Disuse-related bone loss	201
	Reduction in physical activity and associated bone loss	202
	Physical activity and associated bone gain	205
7.1.3	Phases of bone loss	206
7.1.4	Remobilisation	206
7.2	Methodology	208
7.2.1	Biochemical markers of bone turnover	208
7.2.2	Marker of bone resorption - urinary hydroxyproline/creatinine	208
7.2.3	Marker of bone formation – serum alkaline phosphatase	210
7.2.4	Statistical analysis	211
7.3	Results	212
7.4	Discussion	216
7.4.1	Impact of the transplant on bone turnover	216
7.4.2	The effect of the intervention program on bone turnover	218
7.5	Conclusion	222

## **Chapter Eight: Study Five**

### **Changes in QoL following a PBST and participation in an exercise program 223**

	List of abbreviations specific to Chapter eight	224
8.0	Introduction	225
8.0.1	Purpose	226
8.1	Literature Review	228
8.1.1	Quality of life of patients with cancer	232
8.1.2	Exercise and quality of life	235
8.1.3	Relationship between functional capacity and quality of life	238

8.2	Methodology	239
8.2.1	Quality of life assessment	239
8.2.2	Statistical analysis	241
8.3	Results	242
8.4	Discussion	258
8.4.1	Effect of undertaking a PBST on quality of life	258
8.4.2	Effect of a 3-month recovery period on quality of life	261
8.4.2.1	Physical QoL	263
8.4.2.2	Psychosocial QoL	264
8.4.2.3	Medical interaction QoL	265
8.4.2.4	Marital QoL	266
8.4.2.5	Sexual QoL	266
8.4.3	Relationship between functional capacity and QoL	267
8.5	Conclusion	269
 <b>Chapter 9: Summary and Conclusion</b>		<b>270</b>
9.0	Summary	271
9.0.1	Research or clinical implications of working with patients with cancer	278
9.0.2	Potential for future research	280
9.1	Conclusion	283
 <b>Appendices</b>		<b>285</b>
I	Queensland University of Technology ethics approval	286
II	Mater Adult Hospital ethics approval	289
III	Wesley Private Hospital ethics approval	292
IV	Subject information letter and package	294
V	Assessment of body composition via the use of the skinfold technique	305
VI	Assessment of perceived exertion via the use of a visual analogue scale	308
VII	Assessment of handgrip strength	310
VIII	CARES QoL questionnaire	312
IX	A summary of items in the CARES questionnaire	324
X	CARES score and profile sheet	326
 <b>Bibliography</b>		<b>329</b>

## List of Figures

---

1.1	Cancer rehabilitation model or optimal functioning plan	18
1.2	Organisation of thesis	25
3.1	Study design	39
3.2	Initial resistance exercises	
	(a) Seated bench press	50
	(b) Lat pulldown	50
	(c) Leg press	50
3.3	Resistance exercises progressively introduced	
	(a) Upright row	50
	(b) Seated shoulder press	50
	(c) Lunges	50
4.1	Skinfold sites	307
4.2	Changes in weight and body composition for the study group (PI & PII), and the control and exercise group (PI, PII & PIII) (mean±SE)	
	(a) Changes in weight	86
	(b) Changes in percentage body fat	87
	(c) Changes in fat mass	87
	(d) Changes in fat free mass	88
	(e) Individual changes in FFM across the testing phases (PI, PII and PIII) for subjects in the control and exercise group	88
4.3	Changes in TEE for four subjects in the exercise group across the testing phases (TEE at each phase for each subject)	89
4.4	Bland Altman Plot displaying the limits of agreement between the skinfold and SLW technique	90
5.1	Visual analogue scale	309
5.2	Borg's 10 point RPE scale	309

5.3	Individual changes in peak aerobic capacity and lower body strength across the testing phases (PI, PII and PIII)	
	(a) Peak aerobic capacity	126
	(b) Lower body strength	126
5.4	Magnitude of change between PII and PIII for the control and exercise group (mean $\pm$ SD)	
	(a) Peak ventilation	128
	(b) Peak aerobic capacity	128
	(c) Peak muscular strength	128
5.5	Comparisons of handgrip strength (average scores between right and left) between the control and exercise group, and age- and sex-matched healthy controls (mean $\pm$ SD)	129
5.6	Comparisons of peak aerobic capacity (ml/kg/min) between the control and exercise group, and age- and sex-matched healthy controls (mean $\pm$ SD)	129
6.1	The link between exercise, psychological status, the endocrine system and the immune system	151
6.2	T cell subset measures at PI and PII for the study group (mean $\pm$ SE)	171
6.3	T cell function at PI and PII for the study group (mean $\pm$ SE)	
	(a) Total positive response to the mitogen	172
	(b) Positive response to the mitogen, adjusted for CD3+ and CD4+ counts	172
6.4	WBC and lymphocyte counts across the phases for the study group (mean $\pm$ SD)	173
6.5(a)	T cell subset and T cell ratio measures across the phases for the study group, and comparisons with normative data (mean $\pm$ SE)	175
6.5(b)	Individual changes in T cell ratio measures across the phases for 2 subjects at PI, PII, I1, I2, I3 (3-months post-PII), I4 (4-months post-PII) and I5 (5-months post-PII)	175
6.6	T cell percentages across the testing phases for the study group, and comparisons with normative data (mean $\pm$ SE)	176

6.7	T cell function across the testing phases for the study group (mean±SD)	
	(a) Total positive response to the mitogen	177
	(b) Positive response to the mitogen, adjusted for CD3+ and CD4+ counts	177
7.1	Individual changes in urinary hydroxyproline/creatinine across the phases for the subjects in the control and exercise groups	214
8.1	Scoring the CARES	240
8.2	Individual changes in total QoL across the testing phases for the subjects in the control and exercise group	245
8.3	Number of endorsed problems in the physical subscales, across the testing phases (mean±SE)	
	(a) Control group data	247
	(b) Exercise group data	247
8.4	Average severity of the endorsed problems in the physical subscales, across the testing phases (mean±SE)	
	(a) Control group data	248
	(b) Exercise group data	248
8.5	Medical interaction QoL measures for the study group (PI & PII) and the control and exercise group (PI, PII & PIII) (mean±SE)	
	(a) Global score	250
	(b) Number of endorsed problems	250
	(c) Average severity of the endorsed problems	250
8.6	Marital QoL measures for the study group (PI & PII) and the control and exercise group (PI, PII & PIII) (mean±SE)	
	(a) Global score	251
	(b) Number of endorsed problems	251
	(c) Average severity of the endorsed problems	251
8.7	Sexual QoL measures for the study group (PI & PII) and the control and exercise group (PI, PII & PIII) (mean±SE)	
	(a) Global score	252
	(b) Number of endorsed problems	252
	(c) Average severity of the endorsed problems	252

8.8	Comparisons of total QoL and QoL domain measures at PII between the study group and normative cancer data (mean±SD)	255
8.9	Comparisons of total QoL and QoL domain measures at PIII between the control and exercise group, and normative cancer data (mean±SD)	
	(a) Control group	255
	(b) Exercise group	255

## List of Tables

---

2.1	Review of literature concerning exercise intervention and cancer	32
3.1	Group characteristics	46
3.2	Timing of medical events and testing phases	47
3.3	Intervention variables for the control and exercising group	52
3.4	Representation of the data set commonly dealt with during statistical analysis	53
4.1	Dietary intake questionnaire	81
4.2	Body composition and energy expenditure measures at PI and PII for the study group (mean $\pm$ SE)	83
4.3	Body composition measures across the testing phases for the control group (mean $\pm$ SE)	84
4.4	Body composition and energy expenditure measures across the testing phases for the exercise group (mean $\pm$ SE)	85
4.5	Pearson correlation of percentage body fat techniques	90
4.6	The number of patients consuming a certain quantity of major food group servings per day over the past week	92
5.1	Aerobic capacity and strength measures at PI and PII for the study group (mean $\pm$ SE)	123
5.2	Aerobic capacity and strength measures across the testing phases for the control group (mean $\pm$ SE)	124
5.3	Aerobic capacity and strength measures across the testing phases for the exercise group (mean $\pm$ SE)	125
5.4	Aerobic capacity and strength measures at PIII for the control and exercise group (mean $\pm$ SE)	127
7.1	Biochemical markers of bone turnover	193
7.2	Bone turnover measures at PI and PII for the study group (mean $\pm$ SE)	212

7.3	Bone turnover measures across the testing phases for the control group (mean±SE)	213
7.4	Bone turnover measures across the testing phases for the exercise group (mean±SE)	214
7.5	Correlations of the bone turnover measures	215
8.1	Cancer-related QoL questionnaires	230
8.2	QoL measures at PI and PII for the study group (mean±SE)	242
8.3	Physical subscale measures at PI and PII for the study group (mean±SE)	243
8.4	Total QoL measures across the testing phases for the control and exercise group (mean±SE)	244
8.5	Physical QoL measures across the testing phases for the control and exercise group (mean±SE)	246
8.6	Psychosocial QoL measures across the testing phases for the control and exercise group (mean±SE)	249
8.7	Comparisons between the control and exercise group at PIII, for total QoL and QoL domain measures (mean±SE)	253
8.8	Comparison between the control and exercise group at PIII for the physical subscale measures (mean±SE)	254
8.9	Relationship between functional capacity (aerobic capacity in ml/FFM/min) and QoL measures of the study group at PI, PII and PIII	256
8.10	Relationship between the level of change in functional capacity (aerobic capacity in ml/FFM/min) and QoL measures between PII and PIII	257

## List of Abbreviations

---

The following represents a list of abbreviations that can be found throughout all chapters of this thesis. However, a list of abbreviations specific to certain chapters have also been compiled and are presented at the beginning of all relevant sections.

ACSM	American College of Sports Medicine
BC	Breast cancer
BMT	Bone marrow transplant
CG	Control group
CR	Cancer rehabilitation
CSF	Colony stimulating factors
CT	Chemotherapy
EG	Exercise group
GVHD	Graft versus host disease
HDC	High-dose chemotherapy
HR	Heart rate
HRmax	Maximum heart rate
HRR	Heart rate reserve
I1	Intervention 1
I2	Intervention 2
OFF	Optimal functioning plan
PBPC	Peripheral blood progenitor cells
PBST	Peripheral blood stem cell transplant
PI	Phase I
PII	Phase II
PIII	Phase III
QoL	Quality of life
QUT	Queensland University of Technology
REMM	Random effects mixed model
RM	Repetition maximum
RM-ANOVA	Repeated measures analysis of variance
RPE	Rating of perceived exertion
RT	Radiotherapy
SD	Standard deviation
SE	Standard error
SG	Study group
VO <sub>2</sub> max	Maximal aerobic capacity

## Statement of Original Authorship

---

The work contained in this thesis has not been previously submitted for a degree or diploma at any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference has been made.

Date:..... *23/8/01* .....

## Abstracts Arising from Thesis

---

Hayes, S. C., P. S. W. Davies, A. W. Parker, A. Green, and J. Bashford. Exercise in the rehabilitation phase of peripheral blood stem cell transplant patients. *Medicine and Science in Sports and Exercise*. 32:S234, 2000.

Hayes, S. C., P. S. W. Davies and A. W. Parker. Changes in energy expenditure following cancer treatment and an exercise intervention program. *Pre-Olympic Congress. International Congress on Sport Science. Sports Medicine and Physical Education. Book of Abstracts*. Brisbane, p480, 2000.



## List of Acknowledgements

---

This study would not have been possible without those who agreed to participate (and their respective partners) – those whom I now consider my friends. They were a continual source of strength, encouragement, and friendship, and always reminded me ‘to smell the roses’, and ‘recognise what’s important in life’. I can only hope that I gave them as much as they gave me. To Will, Kristie, Jenny and Jillian, your smiling face is missed.

To Ash, Becca and mum - you have given encouragement and kindness; guided, listened and cared; and showed understanding, compassion, and an ever-enduring friendship - for this, I will always be thankful.

I would also like to acknowledge Associate Professor Peter Davies, Professor Tony Parker, Dr David Rowbottom, Dr John Bashford, Connie Wishart, and Grace and Paula at QIMR, for their academic and personal support.

Finally, I would like to dedicate this thesis to my father, George Hayes, who died from bowel cancer, aged 42.

# CHAPTER ONE

## INTRODUCTION

*“Cancer is a word, not a sentence” (Author Unknown)*

## **1. Introduction**

---

Exercise has been prescribed since the fifth century BC when Hippocrates stated that “Eating alone, will not keep a man well; he must also take exercise. For food and exercise, while possessing opposite qualities, yet work together to produce health”<sup>242</sup>.

A general consensus now exists that both regular physical activity and a moderate to high level of aerobic fitness are associated with a reduction in chronic disease morbidity<sup>283</sup> and all-cause mortality<sup>242</sup>. Dr William Foege, former Director of the Centers for Disease Control in Atlanta, USA, suggested that “physical activity may provide the shortcut we in public health have been seeking for the control of chronic diseases, much like immunization has facilitated progress against infectious diseases”<sup>242</sup>. It is believed by many authorities that 50-80% of chronic diseases could be prevented or at least postponed by exercise, proper nutrition, weight control, smoking cessation and stress management<sup>326</sup>.

Suggested mechanisms that link a physically active lifestyle to a reduction in all-cause mortality include a decreased incidence of heart disease and a reduction in certain forms of cancer<sup>110</sup>. It is also associated with a reduction in the length of the terminal period of partial and total dependency<sup>346</sup> and an enhanced quality of life<sup>445</sup>. In addition to these associations, participation in regular exercise leads to other health benefits such as improved cardiovascular<sup>114, 119</sup> and musculoskeletal function<sup>351</sup>, development and maintenance of joint flexibility<sup>6</sup> and psychological benefits<sup>270</sup>. Furthermore, beneficial changes in haemodynamic, metabolic, hormonal, respiratory and neurological function have been reported with improved exercise capacity<sup>119</sup>. In general, exercise has been shown to improve health and wellbeing, enhance functional capacity and the ability to perform daily activities, and in turn, quality of life, while reduce the risk of developing chronic and debilitating conditions. Just as numerous health benefits have been related to a physically active lifestyle, the relationship between sedentary living and a higher incidence of particular lifestyle diseases has also been shown.

### **1.0.1 Physical activity participation rates**

Despite the well-documented association between physical inactivity and the prevalence of adverse health, participation in physical activity remains considerably low<sup>242</sup>. The public health burden is significant because more people are at risk of physical inactivity than any other single risk factor for chronic disease. In response, several countries including the United States have established national objectives to reduce sedentary lifestyles and to increase moderate daily physical activity levels in children, adolescents, adults and the elderly. Unfortunately, evidence from the US initiative showed that many of the goals related to physical activity and fitness were not met<sup>242</sup>. Poor physical activity participation rates were further highlighted in a more recent American investigation that demonstrated the continued widespread erosion of physical activity patterns with increasing age among adolescents and adults<sup>63</sup>. The results also indicated that although males had somewhat better physical activity patterns than females, the decay in participation rates with age was greater for males when compared to females.

An Australian survey of exercise participation rates estimated that approximately two thirds of the Australian population participated in some form of exercise for recreation, fitness or sport<sup>2</sup>. Thirty-seven per cent of those surveyed chose walking as the preferred type. However, based on the frequency, intensity and duration of exercise undertaken, 69% of adults were classified as sedentary or having low exercise levels.

Physical activity is a modifiable risk factor of lifestyle diseases<sup>33</sup> and these inadequate participation rates highlight the need for policy objectives to improve participation and to promote physically active lifestyles worldwide. In summary, there is considerable evidence of the benefits of exercise to both physical and psychological health. Moreover, there exists a plethora of evidence highlighting the role of exercise in the prevention of certain lifestyle diseases, and the benefits attained through physical activity in individuals with cardiovascular disease, hypertension, rheumatic disease, diabetes mellitus, pulmonary disease and renal disease. However, specific information concerning the benefits to cancer patients

and the nature, type and intensity of exercise required to optimise these benefits, is limited.

## **1.1 Cancer**

Cancer refers to more than 100 different disorders all characterised by disturbances in cell growth and development control<sup>165, 376</sup>. It involves a multistage process of initiation, promotion, progression and metastasis, with complex origins involving genetic, environment and gene-environment interactions. Cancer is not one disease, but rather a grouping of diseases characterised by invasive, metastatic cell proliferation, with each having a distinct etiology and pathology.

### **1.1.1 Cancer incidence and mortality rates**

The second leading cause of morbidity and mortality in the United States, accounting for more than 20% of all deaths, is cancer<sup>326, 350</sup>. Each year, approximately 1 300 000 people in the US are diagnosed with cancer and approximately 500 000 people will die from the disease<sup>147</sup>. Although the lifetime probability of developing cancer is greater in males (43.48%) than females (38.34%), women maintain a higher risk of developing any cancer before 60 years of age<sup>147</sup>.

In 1990 diseases of the circulatory system represented the major cause of death (41.8%) within Australia, with heart disease and cerebrovascular disease contributing to 31.3% and 7.4% respectively<sup>2</sup>. During this same period, cancer contributed to 26.9% of deaths. Since the late 1960s, substantial decreases have occurred in the mortality rates from each of the major vascular causes of death<sup>2</sup>. In contrast, the incidence of cancer has progressively increased. In 1997, malignant neoplasms were associated with 27% of deaths, while ischaemic heart disease and cerebrovascular disease represented 22.5% and 9.4% respectively<sup>1</sup>.

Approximately 80 000 new cancer cases are diagnosed each year in Australia<sup>1</sup> with males experiencing a 1 in 3 and females a 1 in 4 lifetime risk of developing cancer<sup>179</sup>. Tracheal, bronchial and lung malignancies are the leading cause of male cancer deaths (24%), followed by cancer of the prostate (13%) and colon (10%)<sup>1</sup>. Females

are at greatest risk from breast cancer, which accounts for 17% of all female cancer deaths. Tracheal, bronchial and lung cancer (14%) and colon cancer (11%) represent the next most common female cancers<sup>1</sup>. The risk of cancer increases with advancing age<sup>401</sup>, with greater than 83% of cancer deaths occurring over the age of 65 and the highest incidence and mortality rates seen in the 85+ age group.

As technology has advanced, outcomes have improved for many malignancies, and thus survival rates (defined as a relative combined 5-year statistic) from those diagnosed with cancer are progressively increasing each year. US data illustrates that when taking into account all cancer sites, the most recent survival rate estimate is 59%<sup>148</sup>. Additionally, the survival rate estimate is approximately 50-80% for those undertaking 'intensive' cancer treatments, specifically bone marrow and peripheral blood stem cell transplantation<sup>166</sup>. As survival rates continue to rise, addressing research issues such as facilitating recovery post-treatment and improving quality of life, is essential.

## **1.2 Exercise and cancer prevention**

It is now believed that approximately 50-80% of all cancers are related to environmental and lifestyle causes<sup>133, 326</sup>. Therefore a large proportion of these cancers may be prevented through the adoption of health practices including proper nutrition, weight control, exercise, smoking cessation and stress management. Of particular relevance to this thesis is the relationship between exercise participation and risk of cancer.

Physical activity has an inverse relationship with coronary heart disease, whereas its influence on cancer is less clear<sup>281</sup>. However between 1980 and 1990, evidence indicated that physical activity was associated with decreased overall cancer mortality and decreased incidence of specific types of cancer<sup>110, 347, 376</sup>. During the course of a Harvard-based study, it was identified that after adjustment for age and smoking, cancer mortality rates were highest in those who exercised the least<sup>110</sup>. While there is an increasing tendency for investigations to illustrate the protective effect of exercise<sup>162</sup>, currently the exact relationship between physical activity and all-cancer mortality remains controversial.

Evidence for the role of exercise in the prevention of cancer has been derived from studies investigating animals or by classifying human subjects into groups according to their occupational or leisure-time activity and then comparing the incidence of cancer within the different groups. Animal experiments<sup>10, 24, 348, 350</sup> have shown that increased physical activity is associated with a 25-100% retardation of tumour growth in rats. Additionally, the growth, size and metastatic spread of experimental tumours is significantly decreased when exercise training is initiated prior to cancer induction, and when moderate training occurs post-cancer development. Prior to carcinogen treatment, exercised rats elicit a lesser incidence of tumours than their sedentary peers. Moreover, when training is discontinued in cancerous mice, tumour growth accelerates until it matches that of the control animals.

Studies of various occupational groups have attempted to determine the relationship between work-related physical activity and cancer risk. These investigations compare individuals working in physically demanding occupations with those working in sedentary roles. Other studies categorise people's leisure time as 'active' or 'sedentary', and then compare cancer incidence between the groups. While the majority of these investigations illustrated a protective effect on cancer by participating in occupational or leisure activity, particularly for colon cancer, the association was not always shown<sup>447</sup>. In a review regarding leisure time physical activity, it was stated that no pattern of consistency emerged, and in several cases the significance of the association was in the opposite direction<sup>199</sup>.

Investigations of former athletes typically categorise subjects based on previous, rather than current exercise habits and then compare the prevalence of cancer among different groups. Lower mortality rates<sup>299, 339</sup>, higher mortality rates, and no mortality rate differences<sup>324</sup>, have been associated with former athletes when compared to their sedentary peers. Other investigations have found that greater physical activity was associated with a decreased risk of rectal and colon cancer<sup>280</sup>, lower prevalence of breast and reproductive system cancers<sup>125</sup>, but an increased risk of skin carcinoma<sup>111, 151</sup>.

Although each of the above mentioned studies have associated limitations<sup>348, 350</sup>, evidence is mounting to support the notion that participation in physical activity is linked with a reduction in cancer risk. In a number of studies designed to investigate the effects of different types and intensities of activity Hill (1999)<sup>162</sup> indicated that four hours of recreational walking or cycling was associated with protection against colon cancer. Energy expenditure comparable to walking or jogging more than 5.5 miles per day has been reported as necessary to decrease prostate cancer risk<sup>212</sup>. Women who participate in approximately 30-minutes of daily exercise, an amount frequently recommended by authorities, show a substantial reduction in breast cancer risk<sup>29</sup>. In addition, women who are active both recreationally and at work have a 40% risk reduction<sup>403</sup>. Others have found that participation in physical activity of four hours per week reduces the risk of breast cancer by more than 50% when compared with inactive women, while one to three hours of weekly physical activity can reduce risk by approximately 30%<sup>303</sup>. Although the exact volume of activity required to reduce overall cancer risk remains unclear, it seems likely that a threshold of activity exists, whereby lower amounts of exercise are of insignificant benefit<sup>425</sup>.

### **1.2.1 Mechanisms by which exercise may influence the presence/absence of cancer**

The mechanisms by which physical activity might influence the course of cancer has been most frequently studied in colorectal cancer patients. The findings indicate that increased amounts of occupational activity, participation in exercise in adulthood, active recreation and levels of total activity, relate to a lower incidence and mortality from colon cancer<sup>23, 39, 54, 122, 134, 211</sup>. Possible mechanisms of association include a reduction in intestinal transit time, which leads to a reduction in the contact time of potential faecal carcinogens with the colon. Additionally, peristalsis is increased with vagal stimulation and aerobic exercise is associated with an increase in vagal tone. In turn, transit rate is enhanced in the segments of the colon innervated by the vagus nerve. Exercise has also been shown to have a stimulatory influence on the secretion of gastro-entero-pancreatic hormones to levels that improve intestinal motility.

Physical activity has been hypothesised to protect against breast cancer through its effect on endocrine function<sup>125, 163, 251</sup>. A proposed strategy of primary breast cancer

prevention is through reduced exposure of the breast to oestrogen and progesterone, and is based on a series of observations of the effect of physical activity during adolescence on menstrual and ovulatory patterns. Although evidence for such an association is limited<sup>294</sup>, high physical activity has been correlated with late age at menarche, early onset of menopause, anovulation and low body fat. This mechanism has particular appeal because it is not dependent on hormonal manipulation by an exogenous agent<sup>30</sup>. It has also been suggested that the population attributable risk estimates for diet and physical exercise are of similar magnitude to those for family history and reproductive and hormonal factors<sup>386</sup>.

As for breast cancer, hormones may also take an aetiologic role in the prevalence of prostate cancer. Males diagnosed with prostate cancer have higher endogenous testosterone levels compared with healthy controls, and cancerous prostate tissue has been reported to have higher testosterone levels when compared with nondiseased tissue<sup>275, 376</sup>. Additionally, lower testosterone levels have been detected among male distance runners and this may act to reduce the risk of prostate cancer in active men. The physical activity-prostate cancer hypothesis is compatible with the standard treatment regime being anti-testosterone therapy, which acts to reduce testosterone levels to those observed after castration. However, the relatively sparse and inconsistent evidence limits universal support for this hypothesis and more research is required<sup>220</sup>.

Other mechanisms by which exercise may influence the presence of all types of cancer have also been proposed. Cancer is a disease of altered immunology and it has therefore been suggested that the observed effects of exercise in reducing cancer risk may relate to altered immune functioning, where regular and moderate intensity activity may have a favourable effect on the number and functioning of specific immune cells<sup>199, 231</sup>. Exercise can also be used as an effective technique for daily stress management, which may influence the release of catecholamines and the subsequent effect of these hormones on immune system function<sup>417</sup>. Reduction in serum cholesterol levels and body fat are two other mechanisms which have the potential to influence cancer risk, as increased levels of these substances are associated with the production of more potent forms of oestrogen<sup>133</sup>. Regular physical activity may also modify the risk of neoplasia indirectly by initiating other

lifestyle changes such as avoiding smoking or alcohol abuse and the maintenance of a healthy diet.

By contrast, an increased cell division after injury from exercise may enhance the chance of metaplasia, while high intensity activity may suppress immune function<sup>350</sup>. The accumulation of X-irradiation during the diagnosis and treatment of injuries, the consumption of performance-enhancing drugs and excessive exposure to ultraviolet radiation during activities such as swimming, may increase the likelihood of the development of cancers. Furthermore, the shift to oronasal breathing from nasal breathing and the increased ventilatory rate evident during exercise participation may increase the exposure to airborne pollutants and carcinogens.

It seems evident that a simple determination of the possibility of an association between physical activity and a reduction in cancer risk may never be reached, given the multitude of possible initiators and promoters, their interactions and individual characteristics<sup>199, 348</sup>. Even if a positive association is identified, manifestations of cancer in physically active individuals may still arise.

### **1.3 Cancer treatment**

Treatment for cancer is highly varied and ultimately depends on a number of factors including the age of the patient, the location of the tumour, whether the tumour is of haematological or solid nature, and the extent of metastasis. Deciding which option will provide the highest possible cure rate and the highest possible quality of life is the primary objective used when deciding the treatment regime<sup>36, 401</sup>. Treatment choice primarily includes surgery, chemotherapy, radiation therapy, or a combination of the three. Unfortunately, each treatment option has the risk of potential adverse effects that may range from changes in the ability to perform daily activities to major organ dysfunction and secondary cancers, and social and psychological effects<sup>155</sup>.

Currently, surgery maintains a primary role in the therapeutic management of solid tumours and has an essential diagnostic and palliative role<sup>401</sup>. When surgery is not a treatment option, radiotherapy (RT) or chemotherapy (CT) is usually administered. Radiotherapy represents a common form of treatment for malignant tumours and can

be applied locally or regionally. It may be utilised as either symptomatic or recovering treatment<sup>401</sup> and is used alone or in conjunction with surgery and/or CT<sup>241</sup>. Less morbidity and acute mortality is associated with RT and it is a potential treatment option when patients have other pathologies that would increase risk associated with a surgical procedure. Unfortunately, treatment regimes are often lengthy.

The endocrine, renal, immune, cardiovascular, gastrointestinal, pulmonary and musculoskeletal system can sustain late effects from RT<sup>50</sup>. The side effects are directly associated with the body area receiving treatment and the vital organs in that field<sup>241, 413</sup>. The radiosensitivity of the tissue, radiation fractions, treatment timing and energy source may ultimately dictate the intensity of the side effects experienced by the patient. However, it is important to acknowledge that not all side effects are dose-dependent, with a primary example being fatigue. Interstitial pneumonitis, intrapulmonary inflammation, pneumonitis, reduced lung volumes and pulmonary fibrosis are just some of the pulmonary complications affiliated with RT. While pericarditis is the most common cardiac complication associated with RT, other cardiac problems may develop and include myocardial fibrosis and accelerated and radiation-induced coronary artery disease.

The value of CT in lengthening survival and optimising performance status and quality of life has been successfully established<sup>328</sup> and it is therefore considered a central treatment strategy for the management of cancer<sup>51</sup>. The systemic treatment of CT maintains the ability to destroy cells that are in a particular growth or division stage<sup>241, 413</sup>. However, antitumour CT regimes are unable to differentiate between cancerous and 'normal' cells and thus side effects are observed in healthy tissue<sup>241, 401</sup>.

Cardiovascular complications may encompass congestive heart failure, ischaemic changes, myocarditis, cardiac necrosis and dysrhythmias<sup>241, 401</sup>. Hypersensitivity reaction such as anaphylaxis; shaking, chills and febrile reactions; dyspnoea, hypotension and bronchospasm; and urticaria and erythematous rashes, tend to be relatively common (4-30%) in patients receiving particular CT regimes. Since bone marrow elements are rapidly dividing, these cells are particularly vulnerable to

destruction by CT or RT, and therefore myelosuppression encompasses a common side effect. Pneumonitis, pulmonary edema, and methotrexate and bleomycin toxicity constitute some of the pulmonary complications that are associated with CT. Additionally, renal complications and veno-occlusive disease<sup>207</sup>, electrolyte imbalances, and neurological complications including dizziness, headache, slight confusion, seizures, and hallucinations, are other known side effects. Changes in body composition and gastrointestinal side effects such as enteritis, typhlitis, nausea, vomiting, and diarrhoea, have also been associated with this treatment option.

### **1.3.1 Bone marrow transplantation and peripheral blood stem cell transplantation**

Irradiation and some cytostatic drugs elicit a steep dosage-versus-antitumour effect relationship, with a correlation existing between the higher the dose, the more effective eradication of the malignant cells. However, due to the toxicity on normal tissues such as the bone marrow or gastrointestinal epithelium, dosage escalations above 150-250% of the conventional used dosages of drugs are prevented, and therefore CT doses are often insufficient to cure specific cancers<sup>250, 397</sup>. Failure to find exploitable differences between malignant and normal cells have frustrated attempts to develop more effective agents that would allow the highly selective therapy required for tumour eradication. The primary cause of morbidity and mortality with high-dose CT is infection secondary to severe and prolonged myelosuppression<sup>371</sup>.

Optimism has encompassed the growth of new therapies, such as bone marrow transplants (BMT) and more recently peripheral blood stem cell transplants (PBST), following high dosages of anticancer drugs<sup>250, 397</sup>. This enables circumvention of the dosage-limiting effect of bone marrow toxicity, dramatically elevating anti-tumour efficacy. There has been a dramatic increase in the use of BMT over the past decade, with a 51% increase in the number of institutions performing the procedure in the United States<sup>12</sup>.

Peripheral blood stem cell transplantation differs from BMT as it involves the infusion of stem cells, rather than bone marrow, following a high-dose treatment

regime. Peripheral blood stem cells are crucial to the recovery of patients following a transplant since all mature blood cells evolve from these 'mother' cells. Stem cells differ from other blood cells in that they are capable of unlimited self-renewal and differentiation. The role of self-renewal is the ability of the cell to reproduce itself into another identical cell, thus maintaining a steady number of these cell types in the body. Differentiation is the process of generating one or more subsets of mature cells that eventually evolve into erythrocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes or platelets. When stem cells are infused into a patient's bloodstream they have the capacity to migrate to the interior of certain bones, colonise and begin producing immature cells known as committed progenitors. These cells alternatively produce colonies of cells that eventually mature into erythrocytes, leukocytes and thrombocytes.

Patients undergo either an autologous or allogeneic BMT or PBST. The process of an allogeneic transplant requires either bone marrow or peripheral blood stem cells derived from an identical sibling, or less commonly from other human leukocyte antigens (HLA) - matched family donors, or from matched unrelated donors<sup>397</sup>. Given that a proportion of patients do not have a matched donor, increasing numbers of patients receive autologous stem cells taken prior to the administration of high dosage therapy.

More recently, autologous PBST have been performed instead of autologous BMT, and have expanded treatment options for thousands of patients diagnosed with life-threatening diseases. A clear advantage of the use of peripheral blood progenitor cells (PBPC) when compared with bone marrow progenitor cells, is the lack of anaesthesia required for the bone marrow harvest<sup>81</sup>. In addition, decreased incidence of transplant-related toxicities including pulmonary and liver effects may be associated with PBST compared with BMT. When PBPC are used, a faster recovery of haemopoiesis and thus shorter hospitalisation periods exist<sup>397</sup>. Furthermore, autologous PBST resulted in fewer septic episodes, less intensive care admissions, reduced erythrocyte and thrombocyte transfusions, a decline in the use of anti-infectious and parenteral nutrition and less hospital costs when compared with autologous BMT.

Initially only patients with acute leukaemia who failed to respond to standard CT were treated with bone marrow and stem cell transplantation<sup>18, 206</sup>. However, the potential implications for this therapy were expanded as the number of long-term survivors after transplantation increased. Bone marrow transplants and PBST are presently considered a potential cure for acute leukaemia, aplastic anaemia, inborn errors of metabolism, severe immunodeficiency syndromes, and chronic myelogenous leukaemia. Encouraging results have been demonstrated for other life-threatening conditions including Hodgkin's disease and non-Hodgkin's lymphoma, breast cancer, ovarian cancer, brain tumours, multiple myeloma, small cell lung cancer, testicular cancer and paediatric solid tumours such as neuroblastoma<sup>80, 126</sup>. However, the type of disease, the stage to which it has progressed, the responsiveness of the disease to prior treatment, and the patient's age and general physical condition are all factors used to determine whether a patient is considered a suitable candidate for a PBST.

With the exception of leukaemia, diseases treated by PBST are primarily not disorders that start in, or involve, bone marrow. Rather they are 'malignant' or cancerous tumours located elsewhere in the body that are responsive to treatment with high-dose CT and/or RT. However, as previously noted, the doses required to destroy the cancer, also destroy the patient's bone marrow. Therefore, without the PBPC, the ability to manufacture blood cells needed to defend against infection, transport oxygen and prevent bleeding is adversely affected<sup>397</sup>.

The process of undertaking a PBST has been divided into four primary stages and includes<sup>397</sup>: progenitor cell harvest; cryopreservation of harvested cells; pre-transplantation chemotherapy and/or radiotherapy; and reinfusion of the cryopreserved stem cells to 'rescue' the patient from bone marrow toxicity.

The ability to obtain sufficient stem cells to restore haematological function and successful pre-transplant treatment of the patient, is a prerequisite for successful PBST<sup>397</sup>. Mobilisation of PBPC may be accomplished by using CT, RT, colony stimulating factors (CSF), alone or in combination with particular CSF or interleukin-3.

Initially the patient is usually treated with a standard-dose CT<sup>397</sup> and once the tumour burden has been minimised, peripheral stem cells are collected after cytokine mobilisation through one or more aphaeresis procedures<sup>126</sup>. The process of extracting stem cells from the bloodstream (peripheral stem cell harvest) is performed with the patient being connected to an aphaeresis device. Hospital admission is usually two to four days and, in order to provide for adequate venous access, a two lumen dialysis catheter is implanted. However, the procedure may be performed using conventional infusion needles if peripheral vein catheters permit. During the harvest, patients may experience symptoms including lightheadedness, coldness, numbness around the lips, or cramping in the hands. Typically, one to three leukopheresis sessions are necessary, with each session taking approximately three to four hours and processing nine litres of blood. Once the stem cells have been collected, the cells are preserved using a cryopreservation process.

The tumour type being treated dictates the type of antitumour CT or RT administered<sup>397</sup>. However, most transplantation schemes are given over three to six days, with a 'washout' period of one or two days prior to infusion of the stem cells. The transplantation process begins with an intensive course of high-dose CT, called the 'conditioning regimen'. The primary objective of this component is to destroy any residual malignant cells in the patient's body, and then the 'tumour-free' marrow or the stem-cells are used to 'rescue' the patient from the high-dose CT/RT damaging and lethal effects<sup>126</sup>. The results of this conditioning regimen is a period of profound pancytopenia, and severe and absolute neutropenia<sup>371</sup>, with significant risk of infections and cytotoxic side effects, ranging in intensity from minimal to life-threatening.

Approximately one to two days later, following the administration of high dosage treatment, stem cells are reinfused by transporting the stem cell solution to syringes and administering it by intravenous bolus or by infusion<sup>397</sup>.

During the first four to five weeks after transplantation, the appearance of the first neutrophil, the presence of the higher absolute neutrophil counts and platelet recovery usually occurs, with the rate of recovery of this initial phase being related to the number and quality of mature progenitor cells infused<sup>371</sup>. A more stable and

complete haematopoietic recovery is generally associated with the subsequent phases, and is secondary to the transplantation of intermediate and early progenitor stem cells, or to the persistence of similar endogenous cells. This latter phase occurs beyond five weeks post-transplant<sup>106</sup>.

Patients are usually characterised as thrombocytopenic and granulocytopenic during the first weeks post-transplantation<sup>397</sup>. The duration of absolute neutropenia is often correlated with the incidence of infectious complications due to the intensive CT regimen<sup>371</sup>. Normal leukocyte and platelet levels are usually observed approximately two to three weeks post reinfusion. However, patients continue to be at increased risk of developing infections during the first few months despite normal leukocyte levels.

The American Society of Clinical Oncology (1994)<sup>20</sup> noted that standard practice in protecting patients against CT-associated infection has been CT dose modification or dose delay, selective use of prophylactic antibiotics, or the administration of progenitor cell support. However, improved supportive care methods have arisen with the inclusion of the use of growth factors or CSF. This assists haematopoietic recovery<sup>137</sup>, reduces the duration of profound neutropenia<sup>371</sup>, reduces the number and duration of the peripheral stem cell harvest sessions, decreases the risk of infection and febrile events and therefore reduces the number of hospitalisation days. Although growth factors significantly accelerate neutrophil recovery and reduce hospitalisation, there is no significant effect on the number of septic episodes and febrile days, or the recovery of platelets<sup>371</sup>. Furthermore, CSF are worthwhile in improving neutrophil recovery past the presence of the first granulocyte, but have no consequence on the length of period during which granulocytes are absent<sup>397</sup>.

Although the success of cancer treatment is continually improving, this success has not been without cost<sup>272</sup>. Increased risk of late physical effects of treatment, social consequences and psychological sequelae have been ascertained as significant issues adversely affecting patients' quality of life. Neitzert and colleagues (1998) in Courneya et al (2000)<sup>80</sup> noted that cytopenias, asthenia, functional capacity losses, sleeping difficulties and psychological distress, comprise some of the acute and chronic side effects that can be experienced by BMT patients. Body image,

relationship, reproductive and fertility changes, work-related fears, the issue of insurance, and questions regarding existential and spiritual well-being, constitute other issues that must be dealt with by patients undergoing cancer treatment<sup>155</sup>. Reduced physical performance and fatigue have also been identified as universal problems following a BMT and are known limitations on the ability to perform occupational and leisure activities, making it difficult to resume normal daily lives<sup>101</sup>. Forty percent of BMT patients require a year to fully recover their physical functioning, and 30% of patients are unable to return to work within the first two years post-transplant<sup>105</sup>.

#### **1.4 Cancer rehabilitation**

Consistent evidence illustrates that cancer patients are likely to experience a decline in their physical and psychological functioning, and that this deterioration in function may persist for months, following treatment<sup>77</sup>. Therefore, the need for intervention strategies that will assist in mitigating the effects of diagnosis and treatment on quality of life and/or hasten recovery is obvious<sup>77</sup>. Increased survival rates have placed more attention on the need for effective rehabilitative procedures<sup>50, 121, 429</sup> and cancer rehabilitation has emerged as a specialisation within both oncology and rehabilitation<sup>121</sup>. Although cancer rehabilitation (CR) has been recognised as an essential component of cancer care, few programs provide effective rehabilitation programs that address both functional and psychological issues<sup>181</sup>.

The rehabilitation process has been considered as “accommodation, or adjustment to personal needs for survival”<sup>100</sup>. The dynamic process of rehabilitation should be directed toward the goal of enabling persons to function at maximum levels in all life domains, within the limitations imposed by cancer<sup>107</sup>. The Oncology Nursing Society defined CR as “a process by which individuals, within their environments, are assisted to achieve optimal functioning within the limits imposed by cancer”<sup>41, 237</sup>. This definition broadened the pool of candidates, the scope of the required needs and interventions, and allowed CR to be considered a conceptual approach as well as a specific program that addresses survivorship issues.

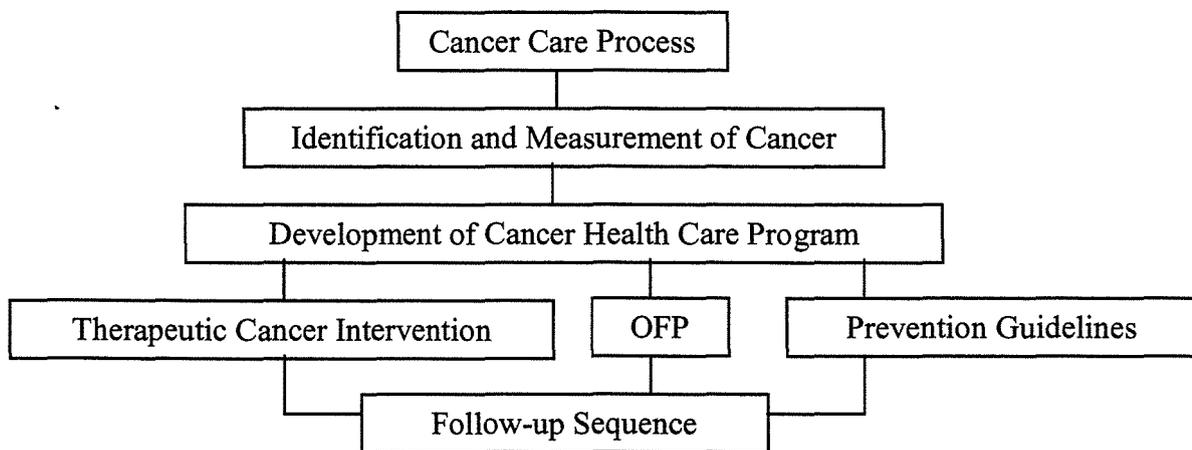
Watson (1990)<sup>414</sup> believes that a global definition is required for the advancement of cancer care. One such definition where “cancer rehabilitation is a dynamic, health-oriented process designed to promote maximum levels of functioning in individuals with cancer-related health problems”, would be appropriate, since all cancer patients are encompassed under this broad definition. Although others<sup>129, 181</sup> have supported this definition, it was also noted that a contemporary cancer rehabilitation program must be designed with an emphasis on all facets of wellness. Therefore, CR should consider any aspect of an individual’s quality of life that is affected by cancer and its treatment. This may include such factors as psychological and social functioning, work-related issues, sexual functioning, nutrition, exercise and fitness, and pain and symptom management<sup>41, 129</sup>.

Dietz (1981) in Watson (1990)<sup>414</sup> introduced the notion of adaptive cancer rehabilitation which consisted of four primary categories: preventive, which aims to optimise physical functioning while reduce morbidity and disability; restorative, which refers to the control, circumvention or elimination of neoplasia; supportive, which is the type of rehabilitation implemented in those patients who will experience periods of remission or control of their cancer, but never ‘cure’; and palliative, which is utilised when the disease is active and advanced, with the aim being to attenuate the disability.

Adaptive CR was then later modelled by Watson (1992)<sup>415</sup> (Figure 1.1). The model depicts that CR or an optimal functioning plan (OFF) is a process that begins with a diagnosis, and is continued until the optimal level of functioning is achieved and maintained. Once disease parameters have been identified, a cancer health care program is developed whereby treatment options are discussed and initiated. Concurrently, an optimal functioning plan is developed to ensure the promotion of rehabilitation throughout the entire cancer care process. At the same time prevention guidelines are developed and may relate to the prevention or reduction of secondary problems stemming from the cancer and its treatment, and/or longer-term prevention via the implementation of positive health promoting behaviours in the patient and family.

The design and implementation of a follow-up health plan completes the model<sup>415</sup>. Follow-up practices should consist of various time fixed activities in which an active role is taken by the patient. During this period, emphasis is shifted from a disease focus and placed on health issues.

**Figure 1.1** Cancer rehabilitation model or optimal functioning plan



The OFP centres on attaining the maximum physical function, adequate and sustained nutritional intake, a practical level of independence in performing daily living activities, an optimistic yet realistic outlook, and effective management of the cancer phenomena<sup>415</sup>. Additionally, the physician and other rehabilitation health care team members need to anticipate sequelae and initiate preventive strategies to alleviate or minimise side effects that will influence a patient's quality of life<sup>129</sup>. Where appropriate, the primary aim should be to restore the patient to functioning levels that existed prior to cancer diagnosis which may include returning the patient to work, school, domestic activities, and social interaction. For those patients where this goal is unrealistic, the principal aim should be to return the patient to their maximal functioning level, to relieve any discomfort, increase mobility and promote independence<sup>41, 161, 444</sup>.

Regardless of what model is applied to cancer rehabilitation, a number of defining attributes can be applied:

- quality and not quantity of life should be the primary concern;
- the patient's needs govern the activity prescribed and performed;
- optimal functioning and independence are principal concerns;
- the process is dynamic, and relevant at any stage of the disease process; and
- the patient must maintain a sense of control<sup>168</sup>.

Finally, CR aims to achieve positive outcomes for all patients with the belief that when a patient is optimally functioning, the individual is experiencing the best possible quality of life.

While a number of cancer rehabilitation programs are in place, the development of these services has been notably slow<sup>154</sup>. A review of cancer rehabilitation programs performed nearly 20 years ago identified that patient education was the primary feature in all programs studied<sup>154</sup>. Unfortunately, many years later, the 'typical' cancer rehabilitation program still does not include physical exercise<sup>388</sup>, is predominantly psychologic in nature and is less likely to appropriately address the physical and functional side effects experienced by the cancer patient<sup>77</sup>.

#### **1.4.1 Exercise as a component in cancer rehabilitation**

Exercise pre-, during and post-treatment has been recommended since 1975, for those with cancer to prevent the sequelae of disuse and to maintain functional capacity<sup>405</sup>. It has also been suggested that, regardless of the level of disability, all individuals should be encouraged to participate in an activity program that is designed to meet their specific requirements<sup>290</sup>. Unfortunately, empirical data concerning the place of exercise in the rehabilitation or palliative care of the cancer patient is lacking<sup>227, 350</sup>.

Ideally, cancer treatment should be initialised and completed with the patient in the best physiological and psychological condition possible. The benefits of exercise will enhance the likelihood of increased endurance throughout the rigours of cancer treatment, and greater independence post-treatment<sup>426</sup>. The vicious cycle of

depression, hypokinesia and progressive tissue loss could be broken through participation in a moderate exercise program<sup>353</sup>. An increase in physical activity may stimulate appetite, assist in the conservation of lean tissue, reduce the speed of the clinical course of the disease, optimise functional capacity, increase the age at death and improve the remaining quality of life<sup>350</sup>. A review of physical exercise and cancer research<sup>124</sup> demonstrated that improvements in functional capacity, body composition, nausea, and fatigue were physiological changes. Positive outcomes in locus of control, mood states, self-esteem and psychological well-being, were identified as psychologic changes associated with participation in physical activity.

Exercise provides a structured and purposeful daily activity<sup>415</sup>, which increases opportunities for social interaction, creates a tone of optimism and promotes overall wellness<sup>181</sup>. Patients may view exercise participation as a means by which they maintain a certain degree of control and responsibility over the course of their treatments, unlike their perceived/real degree of control in the decision-making process of other treatment options. Greater than 50% of people diagnosed and treated for cancer resume active lives<sup>226</sup>. Specific health programming during cancer care would benefit these patients in 'bridging the gap' between treatment cessation and returning to a 'normal' life.

#### **1.4.2 Lack of referral**

The development of rehabilitation strategies is potentially being hindered by health professionals and family members who may advise patients to 'take it easy' and 'get plenty of rest'<sup>425</sup>. Traditionally, cancer programs are only offered to those with obvious cancer-related disabilities, rather than to all diagnosed cancer patients<sup>414</sup>. Given that the success of rehabilitation efforts is potentially dependent on effective rehabilitation programs, team communication and referral patterns<sup>154</sup>, it is important to promote the potential benefits derived through cancer rehabilitation programs to the community and appropriate health professionals.

The theory of planned behaviour states that people will intend to perform a behaviour when they evaluate it positively, perceive it to be under their own control, and believe that important others think the behaviour will be of benefit (Ajzen, 1991, in

Courneya & Friedenreich, 1999<sup>79</sup>). Research findings derived from patients with breast cancer have suggested that lack of personal experience with the situation may mean that patients are more likely to rely on the views of significant others when deciding on behaviours that should be adopted<sup>79</sup>. In clinical populations, it seems plausible to suggest that health professionals, particularly treating clinicians, would be perceived as important others. Thus encouragement from these individuals is essential in facilitating participation in post-cancer treatment care such as exercise. Interestingly, 60% of a breast cancer population studied reported that their physician failed to mention exercise as an important rehabilitative strategy<sup>442</sup>.

The efficacy and cost-effectiveness of cardiac rehabilitation has been proven, yet it still remains an underutilised and poorly referred form of cardiac care<sup>86</sup>. Reasons such as limited access and funding, professional scepticism regarding the efficacy of the program and the provision of risk-factor modification by the treating physician (making formal rehabilitation appear unnecessary) are given for low referral rates<sup>86</sup>. This highlights not only the need for continual research in cancer rehabilitation but also the importance of health professionals' support. Greater emphasis on rehabilitative measures by health professionals is required to ensure that each cancer patient is assisted in achieving their ideal possible function given their limitations and environment<sup>243</sup>. Once referral has been given, continual encouragement is necessary to ensure that patients will act on recommendations<sup>129</sup>. "Physicians have the opportunity and responsibility to promote regular physical activity"<sup>119</sup> with regard to the 'normal' population. It has also been reported that "Physicians should routinely refer and vigorously encourage"<sup>228</sup> cardiac patients to participate in rehabilitation programs. While cancer rehabilitation research might still be considered preliminary, there is sufficient evidence to support the use of these two quotes within the cancer domain.

## **1.5 General research purpose**

Convincing evidence demonstrates that undergoing cancer treatment induces numerous physiological and psychological effects that may lead to a dramatic influence on quality of life. Most work cited in the area of exercise and cancer rehabilitation has investigated breast cancer patients who have undergone conventional treatment regimens. This investigation sought not only to investigate a unique cancer patient population, but to also study a population subjected to extensive and intensive cancer treatment. Peripheral blood stem cell transplant patients have often undergone conventional treatment prior to undertaking high-dose chemotherapy and/or radiotherapy followed by PBST. It is therefore a purpose of this thesis to determine the functional side effects of a PBST. Additionally, the effect of the transplant procedure on quality of life will be considered and investigated.

Evidence of the positive response of cancer survival rates to various treatment strategies including exercise, provides a background to another purpose of this investigation which was to evaluate the potential of exercise to enhance post-treatment recovery and quality of life. Specifically the investigation will:

Objective 1:

To investigate changes between pre- and post-transplant measures of functional capacity and quality of life.

*Research hypothesis for primary objective 1:*

Functional capacity and quality of life decreases following a PBST (as determined via pre- and post-transplant measures).

Objective 2:

To investigate the role of a three-month duration, moderate intensity and mixed type exercise program in the recovery of functional capacity and quality of life, post-PBST.

*Research hypothesis for primary objective 2:*

Exercising PBST patients experience a faster recovery of functional capacity and quality of life, when compared with non-exercising patients (as determined by pre- and post-exercise intervention measures).

Objective 3:

To investigate the relationship between functional capacity and quality of life of PBST patients.

*Research hypothesis for primary objective 3:*

Functional capacity is related to quality of life.

Objective 4:

To investigate the ability of PBST patients to participate in, and tolerate the three-month, moderate intensity, mixed type, intervention program.

*Research hypothesis for primary objective 4:*

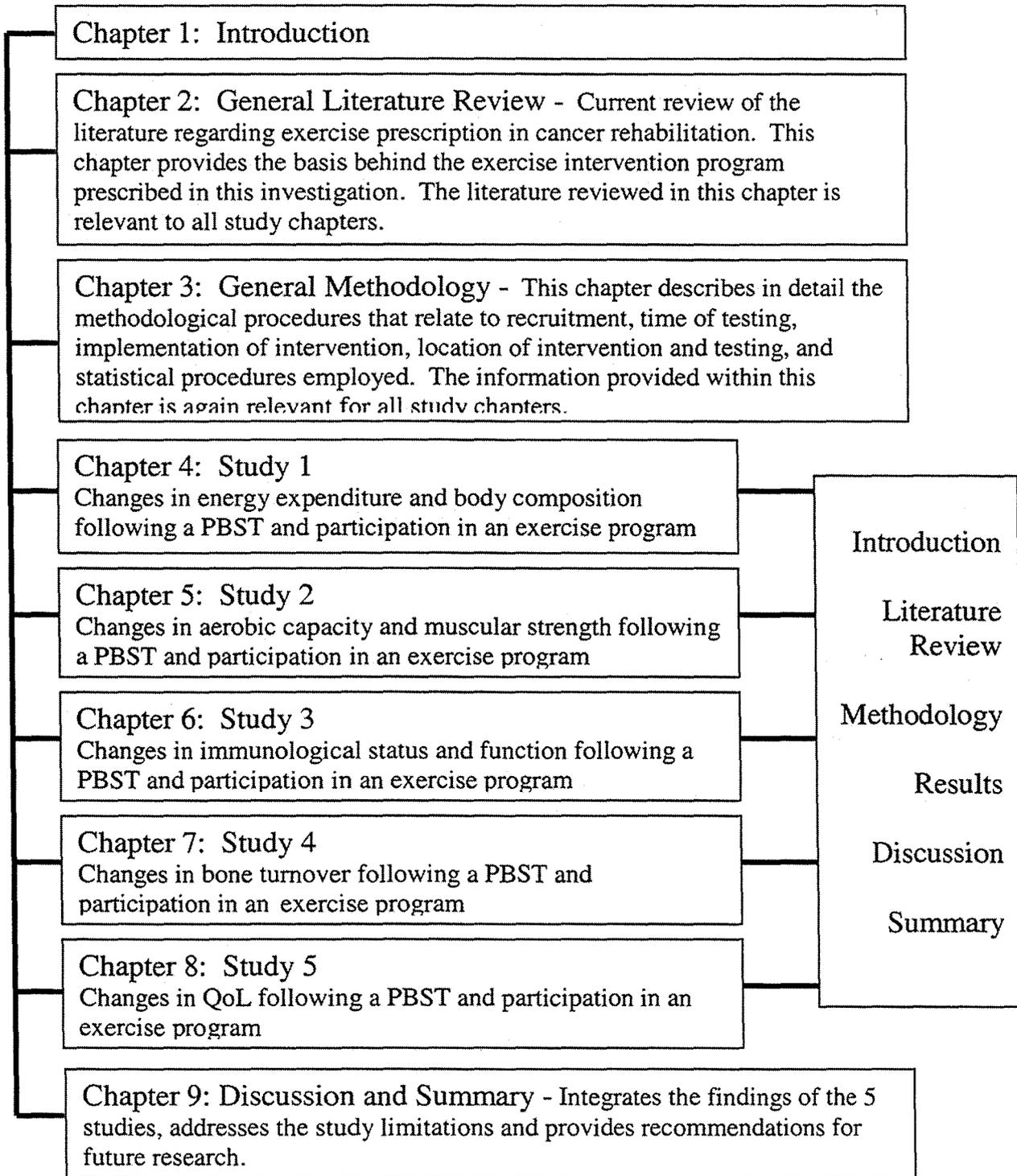
Patients undergoing a PBST can participate in regular exercise following treatment. Further, PBST patients can tolerate an exercise prescription that involves both overload and progression.

In order to meet these objectives, this investigation has been divided into 5 studies, which are extensively covered in Chapters 4 – 8. As noted earlier, this thesis aimed to assess changes in two primary factors, functional capacity and quality of life. Measures of aerobic fitness are predominantly used throughout the literature to determine functional capacity. However, functional capacity is not just aerobic

fitness and many of the side effects reported following treatment may influence functional capacity. Therefore, in order to provide a comprehensive assessment of functional capacity, several physiological measures were included - aerobic capacity, muscular strength, body composition, energy expenditure, immunological changes, and bone turnover. The final study involved the assessment of quality of life, and determined the relationship between functional capacity and quality of life.

This thesis has been organised to firstly provide a literature review and general methodology that are relevant to all measures assessed (Chapter 2 & 3). More specifically, Chapters 2 and 3, address the available literature regarding exercise prescription for cancer patients, and provide reasoning for the exercise prescription implemented in the intervention program. Thereafter, the following Chapters address the literature, objectives, methodological procedures, results and discussion, which are specific to each study (Chapters 4 – 8). Finally, Chapter 9 integrates the findings of the five studies and demonstrates how the conclusions drawn from the studies meet the original objectives. The organisation of this thesis has been illustrated in Figure 1.2.

Figure 1.2 Organisation of thesis



# CHAPTER TWO

## GENERAL LITERATURE REVIEW

*“I do not recommend that patients with malignancy jump into an exercise program, walk into it, maybe, but not jump into it”  
Carl Simonton in Uhlenbruck (1991)<sup>394</sup>*

## 2. General Literature Review

---

### 2.0 Introduction

It is well known that the benefits of exercise training are short-lived and that continuous regular exercise is required to sustain long-term health benefits. Research reported by the American College of Sports Medicine (ACSM)<sup>4</sup> illustrates that significant losses in cardiorespiratory fitness occur following only two weeks of detraining and that a 50% reduction in aerobic capacity can occur after only 4-12 weeks of detraining. This detraining effect has significant implications when applied to the cancer population.

Firstly, cancer patients are at risk of a reduction in functional capacity during the period of diagnosis to treatment initiation. The decline in exercise participation and thus the risk of functional capacity losses during this period has been documented<sup>77, 80</sup>. Additionally, BMT patients commonly receive conventional treatment regimens prior to undertaking a BMT<sup>80</sup>. Therefore, the risk of functional capacity losses between the period of cancer diagnosis and BMT initiation is particularly high for these patients.

The second period where patients are at risk of detraining effects, is during the treatment process itself. Exercise participation rates for BMT patients during treatment are low and have been observed via an observational design investigation<sup>80</sup>. Forty percent of BMT patients within this study did not participate in any cycling exercise, and 24% of participants did no exercise at all. Further, for those who did partake in some exercise, the mean daily cycling/walking duration was less than eight minutes.

Functional capacity has been measured following cancer treatment. The exercise capacity of the cancer patient at this stage is in the range of 3-6 metabolic equivalents (METs) (that is, 10.5-20.5 ml/kg/min)<sup>3</sup>. For patients who have undergone a BMT, their MET values have been calculated to be less than 5<sup>101</sup>.

Evidence is available to support the notion that cancer diagnosis, treatment and its associated prolonged bed rest lead to a substantial loss of physical performance, beginning at diagnosis and continuing following treatment. However, the literature also provides data which demonstrates the benefits that can be sustained by cancer patients through exercise participation, throughout all stages of the cancer continuum. The benefits reported by eleven studies investigating the association of exercise and rehabilitation among cancer patients have been summarised by Friedenreich and Courneya (1996)<sup>124</sup>. Improvements in functional capacity (as measured by aerobic capacity), work capacity, heart rates at a given power, maximum workloads, and body composition, as well as beneficial changes in nausea, natural defense mechanism, and fatigue levels were noted. The effects of participation in physical activity are not limited to improved physiological functioning since beneficial changes in feelings of control, independence, self-esteem, self-confidence, social interaction, depression, tension, anxiety and fear have also been documented<sup>105, 247</sup>. Ultimately, these physiological and psychological improvements have led to positive changes in quality of life<sup>80</sup>.

## **2.1 Exercise prescription for cancer patients**

When describing the process involved in developing an exercise regime, Carl Simonton quoted, "I do not recommend that patients with malignancy jump into an exercise program, walk into it, maybe, but not jump into it"<sup>394</sup>. Further, "...if patients can sit in a chair, do not let them lie in bed; if they can walk, do not let them sit"<sup>426</sup>. While exercise has been shown to instigate changes for cancer patients, the exercise variables prescribed, including the type, frequency, intensity and duration of exercise undertaken will determine the degree and nature of these changes.

### **2.1.1 Exercise Variables**

#### **Type**

When determining the type of exercise that is appropriate for the patient factors that need to be considered include safety, patient preference, convenience, platelet counts, and potential bone metastases<sup>425</sup>. The ACSM (1991)<sup>3</sup> recommends that exercise involving large muscle groups and which is rhythmical and aerobic in nature

should be prescribed for patients with cancer. Additionally, non-weight bearing activities are preferable when skeletal or muscle integrity is compromised, and dynamic lifting on machines should be encouraged to enhance muscle strength.

**(a) Aerobic exercise**

Aerobic exercise is primarily prescribed for improvements in cardiorespiratory fitness, cardiovascular efficiency and weight control<sup>3</sup>. One of the best exercise modes for cancer patients is walking, since it constitutes an activity performed regularly during daily activities and is useful in the maintenance of the basic elements of proprioception important for mobility and balance<sup>426</sup>. Due to the upright nature of walking, position dependent dehydration and orthostatic hypotension can be counteracted. Another primary advantage of this type of exercise is that major muscle groups are utilised and that the systems required for energy production (particularly the aerobic energy system) are stimulated. Lastly, it is a convenient mode for patients regardless of age or disease status, and does not require specific exercise materials or equipment. When patients are at risk of stress fractures, cycling or swimming provide good alternatives. During periods of hospitalisation, 'hallway' exercises have been prescribed with the aim of minimising loss of functional capacity<sup>426</sup>.

**Prescription**

A proper assignment of duration, frequency and mode of activity are required for favourable cardiovascular changes and adequate exercise intensity is paramount if oxygen transport is to be sufficiently taxed<sup>35</sup>. While a training intensity consistently 'low', is likely to be ineffectual in eliciting a training effect, the risk of adverse physiological consequences is elevated when exercise is maintained at a consistently high intensity<sup>4</sup>.

An exercise intensity corresponding to 50-85% of calculated maximal aerobic capacity ( $VO_2$  max) or 65-90% of calculated or predicted HR maximum (HRmax) is an effective training stimulus to elicit physiological improvements in cancer patients<sup>3, 425</sup>. For those who are deconditioned following diagnosis and treatment, maintaining a HR intensity of 60% HRmax is sufficient<sup>425</sup>. Calculation of the HR reserve (HRR) is another method of determining exercise intensity. Classifying the

working HR range by using the HRR requires three steps: subtracting the resting HR from the maximal HR to obtain the HRR; then taking 60-80% of the HRR, and finally adding each HRR value to the resting HR to obtain the training HR range<sup>187</sup>. However, since a patient's HRR represents a relatively narrow range<sup>425</sup> and given the possibility of observing unusually high working HR, using a percentage of HRmax may be a more appropriate guide to training intensity, when compared with the HRR method.

The rating of perceived exertion (RPE) scale represents another means of determining workload intensity<sup>35</sup>. The original RPE scale used rankings from 6-20 with a scale of 7 and 19 being reflected as the perception of working at a very, very light intensity, and a very, very, hard intensity, respectively<sup>48</sup>. This scale was revised to an 11 point scale, starting at 0 'nothing at all', and finishing at 10 'very, very heavy (almost maximum)'. Calculation of a RPE involves the integration of signals by the brain, from the peripheral working muscles and joints, and from the central circulatory, pulmonary and nervous systems. These signals, perceptions and experiences are then integrated or summed into a configuration of perceived exertion<sup>35</sup>. Perceived exertion ratings of 12-14, when using the 20 point scale, and 4 on the new scale represent an effective exercise intensity that usually approximates with 70-85% of HRmax. Ratings of 15 or higher, indicate the need for a reduction in intensity<sup>35</sup>. The use of RPE within clinical populations is only effective when all the effort sensations from a training intensity perspective is contingent upon one effort sense not overriding another. If one sensation, such as leg pain, overrides another sensation such as breathing, then use of the RPE scale could potentially be limited<sup>35</sup>.

Caution is required when prescribing unsupervised programs and lower HR ranges of 40-65% of the estimated HRR<sup>426</sup>, or a working intensity corresponding to 60% VO<sub>2</sub> max<sup>161</sup> should be utilised. If the patient experiences an elevated pulse greater than 10 minutes post-exercise or dyspnea during the exercise program, the intensity needs to be reduced<sup>426</sup>. However, symptoms such as these usually only occur when the patient allows their pulse to move outside the suggested target HR range.

When training duration is relatively short and intensity is low, patients should perform exercise more frequently<sup>425</sup>. A strategy presently being applied is the 'half-

rule-of-thumb<sup>426</sup>. This involves assessing what duration and intensity a patient can comfortably tolerate and beginning with half that much, several times of day, with appropriate rest intervals between exercise sessions. This program is then monitored and adjusted to suit the functional capacity of the patient. As function improves, duration lengthens and frequency can be reduced<sup>425</sup>.

The literature suggests that in relation to 'healthy adults', improvements in VO<sub>2</sub> max tends to plateau when frequency of training is increased above three days per week<sup>4</sup>. The value of the added improvement in maximal oxygen uptake is small when training is increased to more than five days per week. In contrast, no meaningful alterations in VO<sub>2</sub> max have been shown when training is less than two days per week. While the majority of exercise and cancer rehabilitation research has applied a three days per week frequency regimen, more research is required to assess whether these principles proven for the 'healthy' population, also apply to cancer patients.

### **Exercise prescription utilised in cancer research**

As noted earlier, Friedenreich and Courneya (1996)<sup>124</sup> reviewed the literature on the association of exercise and rehabilitation among cancer patients. Eleven studies were identified, including two unobtainable unpublished conference proceedings, two doctoral dissertations and seven published research studies. Table 2.1 provides a summary of the work reviewed. Five of these studies employed an exercise intervention utilising a cycle ergometer, three times per week, of intensity between 60-85% HRmax, for a period of 10-12 weeks. One other interventional project implemented a similar design to those already mentioned, using a cycle ergometer, that lasted 4-6 weeks, but also included a 6-month, 2-3 times per week, moderate intensity activity of any type in a supervised setting. The remaining intervention study employed a home-based walking program whereby patients exercised 4-5 times per week, gradually increasing their duration from 10-45 minutes, across a 3-6 month period. One other investigation not included within the review, was performed on autologous BMT patients. This intervention study implemented a 6-week, daily walking program, of 90% maximum HR, starting with a discontinuous duration of 15 minutes, and progressing to a continuous 30 minute duration<sup>104</sup>. It is clear that while various protocols have been employed, the majority of studies have worked within the exercise variables recommended, and have shown promising

results in measures that maintain the potential to enhance functional capacity and quality of life.

**Table 2.1** Review of literature concerning exercise intervention and cancer (adapted from Friedenreich & Courneya, 1996<sup>124</sup>)

Reference	Total Sample Size	Groups within the Study	Design	Exercise Intervention
Winningham, 1983	12	Exercise, Control & Healthy	Quasi-experimental	Cycle ergometer 10-12 wks, 3 x wk, 20-30min, 60-85% HRmax
MacVicar & Winningham, 1986	16	Exercise, Control & Healthy	Quasi-experimental	Cycle ergometer 10 wks, 3 x wk, 20-30min, 60-85% HRmax
Winningham & MacVicar, 1988	42	Exercise, Placebo & Control	Randomised controlled trial stratified by age/functional capacity	Cycle ergometer 10 wks, 3 x wk, Unknown duration, 60-85% HRmax
MacVicar et al, 1989	45	Exercise, Placebo & Control	Randomised controlled trial stratified by functional capacity	Cycle ergometer 10 wks, 3 x wk, Unknown duration, 60-85% HRmax
Winningham et al, 1989	24	Exercise & Control	Randomised controlled trial stratified by functional capacity	Cycle ergometer 10-12 wks, 3 x wk, 20-30min, 60-85% HRmax
Nelson, 1991	108	54 cases: 40 exercisers, 14 nonexercisers 54 controls, 46 exercisers, 8 nonexercisers	Retrospective case-controlled	Health Promoting Lifestyle Profile (self administered questionnaire)
Young-McCaughan & Sexton, 1991	71	Exercisers and nonexercisers	Retrospective cohort	Self administered questionnaire – any activity before and after diagnosis
Peters, 1992	13	Exercise	Quasi-experimental (pre- and post-test comparison)	Cycle ergometer 5 wks, 2-3x's/wk, 60-85% HRmax, + any activity for 6-mths, 2-3 x wk
Mock et al, 1994	14	Exercise & Control	Randomised controlled trial	Walking 4-6 mnths, 4-5 x wk, 10-45 min, own intensity

**(b) Resistance exercise**

Resistance training is an effective means for developing musculoskeletal strength and is often prescribed for fitness, health and the prevention and rehabilitation of orthopaedic injuries<sup>117</sup>. Increases in muscle mass, bone density, connective tissue thickness and associated increases in muscle strength and endurance, constitute the primary physiological adaptations most often associated with resistance training. It

is worth noting that for decades, cardiac rehabilitation programs have focused almost exclusively in improving cardiorespiratory endurance, while ignoring muscular fitness development<sup>404</sup>. Moreover, it was hypothesised that resistance training was potentially hazardous for the cardiac patient due to the risk of cardiovascular complications from adverse haemodynamic responses. Continuing research within this domain now indicates that resistive exercise testing and training are safe and effective for patients appropriately screened, even at relatively high workloads. With reference to cancer patients, it has been cautioned that resistive exercises may result in increased blood pressure and thus elevate the risk for haemorrhage<sup>50</sup>. Therefore, it is essential to ensure blood counts are within normal ranges, particularly platelets, prior to patients participating in a resistance training program.

Everyday lifting, carrying and moving activities require a certain degree of strength. The return to daily vocational and avocational activities is therefore facilitated by improvements in muscular strength for those patients who have lost strength through the disease process<sup>404</sup>. When strength is improved, daily activities can be performed at a lower energy cost and with greater efficiency. Improved work tolerance derived from peripheral adaptations in trained skeletal muscle (increased enzyme activity and intramuscular fuel stores), in conjunction with greater self-confidence and self-image, enhance the ability of patients to resume routine daily activities and to participate in aerobic activities at a lower oxygen cost<sup>404</sup>.

### **Prescription**

The effectiveness of a strength training program depends on several factors, including frequency, volume (the repetitions and sets performed in conjunction with the resistance) and mode (free weights versus variable resistance, dynamic versus isometric, concentric versus eccentric contractions)<sup>117</sup>. One common factor in recent effective strength training and rehabilitation programs has been the inclusion of at least one set of the maximal or near maximal number of repetitions possible for each exercise performed. The greatest strength gains appear to result from resistances yielding 4-6 repetition maximum (RM), while increasing the number of repetitions to 12-20 RM favours the increase in muscle endurance. Programs that emphasise exercising with a resistance that allows 8-15 repetitions are traditionally classified as 'moderate intensity', and are usually recommended for most of the adult nonathlete

populations<sup>117</sup>. The ACSM (1990)<sup>4</sup> noted that 8-12 repetitions per bout of exercise is generally recommended to elicit improvements in both muscular strength and endurance.

The ACSM (1990)<sup>4</sup> and Feigenbaum and Pollock (1997)<sup>117</sup> performed a review of the literature with regard to appropriate strength training regimens. The literature supports the recommendation of prescribing single-set programs performed to fatigue, and identifies that the quality (intensity) of training is more important for developing muscular strength in sedentary people, than the quantity of training. It has therefore been recommended that single set programs are equally effective as multiple set programs in the first three to four months of strength training in previously untrained individuals. In addition, time efficiency is improved when performing single set programs, which should generally translate with greater exercise program compliance.

Muscle recuperation, muscle development and the prevention of overtraining or detraining are dependent on the allocated rest period. Based on current findings, it seems evident that no single optimal frequency of strength training exists for all muscle groups. Current guidelines suggest that a minimum of two, or two to three days per week, is the most appropriate, as this allows time for recuperation, is less time-consuming, improves compliance and produces health and fitness benefits in the untrained person.

In summary, for healthy people under 50 years, the goal is to be able to complete one set of 8-12 repetitions to volitional fatigue. However, guidelines established by the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation for cardiac patients, recommend a lower intensity program that may reduce the risk of orthopaedic injury and which consists of one set of 10-15 repetitions. Depending on patient status, this lower intensity program would be performed to a level perceived as moderate or comfortably hard or to volitional fatigue. Others have also noted that appropriate strength gains can be attained in higher-risk patients, patients with low functional capacity and those who fatigue easily, by performing only one set of 12-15 repetitions for specified muscle groups with no time limit<sup>404</sup>.

Although the side effects of cancer, treatment and bed rest highlight the need for muscle training, no research could be identified that implemented resistance training as part of an exercise intervention design.

### **(c) Mobility exercise**

Mobility, range of motion or stretching exercises are effective in maintaining joint and muscular flexibility, while assisting in the prevention of contractures<sup>429</sup>. These exercises should be integrated in the warm-up and cool-down phases of all exercise sessions and should be performed on days when side effects of the disease and its treatment prevent participation in aerobic or strength training.

### **Progression**

The key to a successful program is starting slowly and building gradually<sup>426</sup>. The goal of progression is to gently exert without reaching exhaustion, by continually adjusting one or a combination of intensity, frequency, or duration. Following a difficult treatment or infectious illness period, an effective starting point must be determined. In order to avoid overexertion, an empiric rule is to advise “wait until you feel better one day, then wait one more day before returning to the regular exercise program”<sup>425</sup>. When resuming the exercise program after a period of rest induced by treatment or hospitalisation, the exertional level should be reduced to that of one week prior to the interruption and HR and RPE should be closely monitored. It has also been recommended that the exertional level should be reduced if the HR is higher than 75% HRmax. A training intensity of 60-75% HRmax should be maintained for a least two sessions, before progressing<sup>425</sup>.

### **2.1.2 Considerations during exercise prescription**

Although exercise prescription guidelines for cancer patients exist, and have been shown to induce benefits, there are a number of important considerations that need to be addressed prior to patients participating in a regular exercise program. Firstly, while many chronic illnesses have a distinct and single etiology, this is not the case for cancer<sup>425</sup>. Adequate knowledge regarding the type of cancer presented, its complications, course and treatments is essential in order to devise safe and effective

exercise programs for cancer patients<sup>3,5</sup>. Prior to exercise testing, the type of cancer needs to be classified, the extent of metastasis determined and the body organs and regions likely to be affected in both the short- and longer-term by the cancer and its treatment should be acknowledged. For example, patients with multiple myeloma, are particularly susceptible to bone fracture, pulmonary tumours may impair gas exchange, while hepatic tumours may alter metabolic and coagulation responses - with all cases having specific implications when designing an exercise program.

Other information required includes:

- patient's previous and current functional status;
- the presence of other illnesses independent of the cancer;
- therapy previously, presently and likely to be undergone and their actual and potential side effects;
- exercise programming implications; and
- the timing of future tests and treatment administration<sup>429</sup>.

A personal history examination should also examine both family and personal history of cardiovascular disease, respiratory diseases, diabetes, obesity, and elevated blood pressure and blood lipid abnormalities. Furthermore, patients should be screened for past and present musculoskeletal problems (prior injuries, prosthesis, bone pain), sensory limitations (difficulty with vision, balance, neuropathies) and any other factor that may influence the development or maintenance of an exercise regimen, including personal health behaviours such as diet and cigarette smoking<sup>3, 369, 426</sup>.

Guidelines and recommendations of an exercise regimen should address the needs of two primary types of patients - those accustomed to previous exercise and those who have led a sedentary lifestyle<sup>429</sup>. Of those patients who were previously active, education regarding the need for appropriate changes to their 'usual' exercise routine is required. These patients are often unaware of how cancer and associated treatments may influence their ability to participate in exercise. For previously sedentary patients, fatigue and/or weakness experienced by partaking in physical activity may be interpreted as evidence of their need to rest or 'take it easy'. Patients should be educated that these symptoms are not inevitable consequences of their illness and treatment.

The exercise physiologist must be familiar with the 'contraindications to exercise' list for cancer patients<sup>5, 426</sup>, some of which include the development of an irregular pulse, resting pulse rate greater than 100bpm, chest pain, pallor and low blood counts. Vigorous activity should be discouraged two-three hours prior to blood analyses, as blood cell counts and serum enzyme levels may be affected<sup>429</sup>. Fever or infection are also contraindications for exercising and the patient should be advised to exercise the day after they feel better<sup>429</sup>. It has been further recommended that patients should refrain from activity on the same day as intravenous chemotherapy<sup>426</sup>. This guideline was based on the findings of one study (Unverferth et al, 1983 in Winningham et al, 1986<sup>429</sup>) which reported a significant increase in cardiac dysrhythmias in the first two to six hours following chemotherapy administration. Blood count levels are considered by many to be a crucial indicator of exercise participation. Most researchers dealing with cancer patients are guided by the following American recommendations<sup>426</sup>: platelet counts should be greater than 50 000/mm<sup>3</sup>, haemoglobin more than 10g/dl, white blood cell counts greater than 3 000/mm<sup>3</sup> and absolute granulocyte counts higher than 2 500/mm<sup>3</sup>. Others, however, have been guided by slightly lower values of platelet counts greater than 20 x 10<sup>9</sup>/L and leukocyte counts above 1.5 x 10<sup>9</sup>/L<sup>104</sup>.

Finally an important consideration relevant to the success of exercise programs and exercise intervention studies is that of program acceptance. Convenience of the program including the duration of the sessions, time of scheduling and location, and the exercising environment such as cleanliness and atmosphere, are likely factors that will influence program acceptance.

In summary, participation in an exercise program has the potential to induce physiological and psychological benefits for patients diagnosed and being treated for cancer. Recommendations for exercise prescription are available and have been shown throughout the literature to be 'appropriate' and 'safe' for certain patient groups, in particular, breast cancer patients. However, due to the nature of the disease process and the treatment options available, it is crucial to consider a number of factors prior to exercise prescription.

# CHAPTER THREE

## STUDY DESIGN AND GENERAL METHODOLOGY

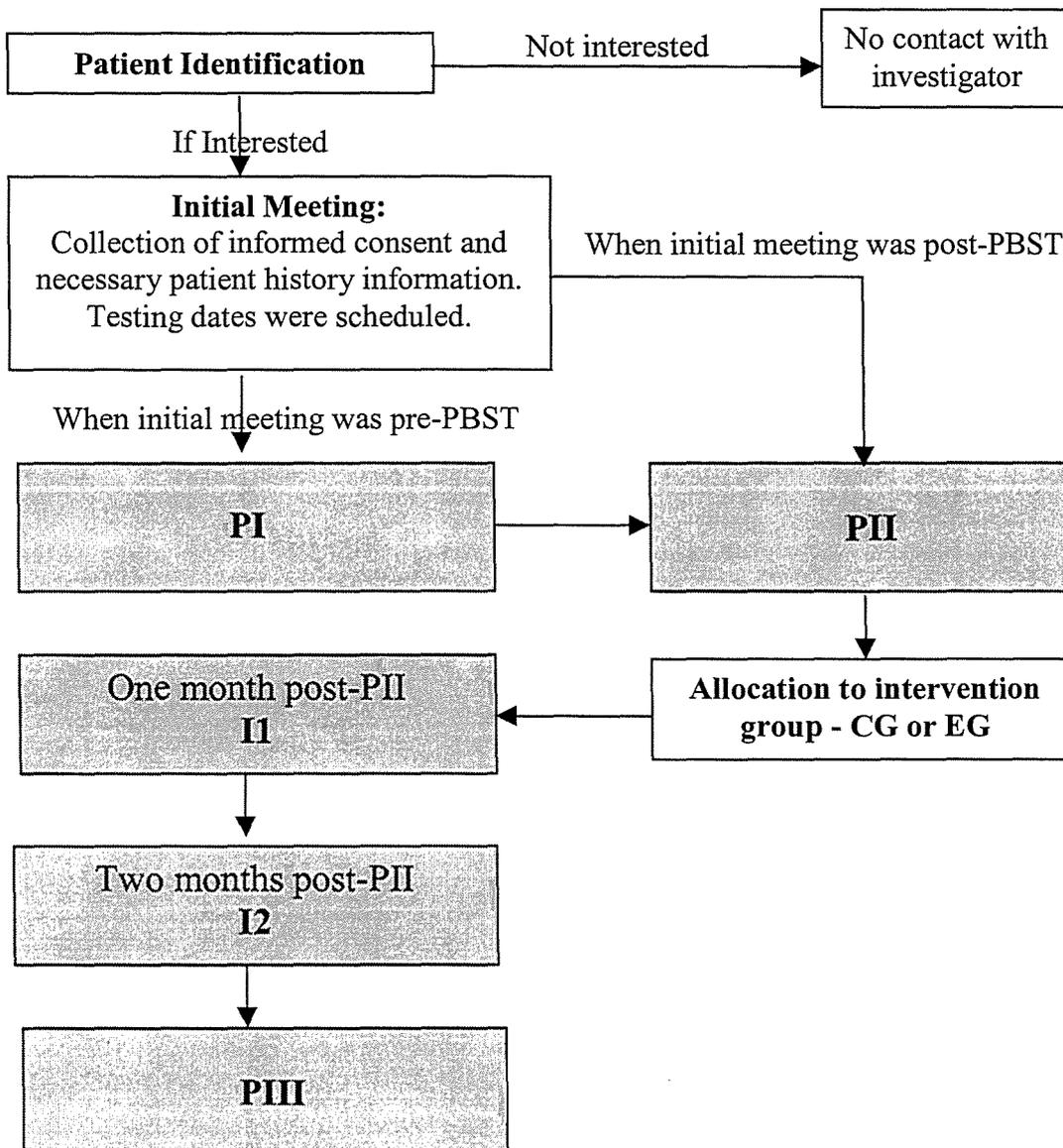
*“Physical activity may provide the shortcut we in public health have been seeking for the control of chronic diseases, much like immunization has facilitated progress against infectious diseases”, Dr William Foege, former Director of the Centers for Disease Control in Atlanta, USA<sup>242</sup>*

### 3. Study Design and General Methodology

#### 3.1 Study design

This study recruited PBST patients and assessed their functional capacity and quality of life at three primary testing phases – pre-transplant (PI), post-transplant (PII) and three months post-PII (PIII). One measure was also assessed at the end of the first and second month of the intervention period (I1 and I2, respectively). Following testing PII, patients entered either the control group (CG) or the exercise group (EG). Figure 3.1 provides a graphical demonstration of the study design.

Figure 3.1 Study design



### **3.2 Patient type**

A primary objective of this investigation was to illustrate that even those cancer patients who undergo ‘high-dosage’ treatment, are still able to participate and tolerate a planned regular exercise program, and could benefit from its implementation. When assessing cancer types and their associated treatment, it is difficult to find a more intensive treatment regimen than an allogeneic or autologous BMT, or PBST. Unfortunately, as was noted in the first two chapters, patients suffer from a number of adverse side effects and can experience major life-threatening complications as a result of undergoing this form of treatment. In turn, it was recognised that these post-transplant complications could potentially hinder the design of an investigation and thus influence the ability to draw research conclusions. Autologous BMT or PBST patients experience fewer post-transplant complications when compared with allogeneic patients. Therefore, in order to meet the primary objectives without jeopardising the project design, it was determined that only autologous patients would be recruited into the study.

As was highlighted in chapter one, initially only patients with acute leukaemia who failed to respond to standard chemotherapy were treated with BMT and PBST<sup>18, 206</sup>. However, BMT and PBST are currently considered a viable treatment option for patients with acute leukaemia, aplastic anaemia, chronic myelogenous leukaemia, Hodgkin’s disease, non-Hodgkin’s lymphoma, breast cancer, ovarian cancer, brain tumours, multiple myeloma, small cell lung cancer, testicular cancer and paediatric solid tumours such as neuroblastoma<sup>80, 126</sup>. Consequently, by studying patients undergoing this procedure, a wide range of cancer patients can be investigated.

### **3.3 Ethical approval of research**

Following an assessment of autologous transplants undertaken each year within two Oncology treating hospitals, it was predicted that the study would be able to recruit from a pool of approximately 80 patients across a one-year period. Ethical approval was sought and obtained from the Queensland University of Technology (Appendix I) and two Brisbane hospitals (Appendix II & III).

### **3.4 Determination of sample size and recruitment of subjects**

When determining the appropriate sample size, a number of factors were considered:

- the primary objectives of the study;
- statistical requirements of 80% power and 5% significance level; and
- the level of physiological change that would be considered both clinically and statistically significant.

Unfortunately, limited data were available throughout the literature to assist in determination of an appropriate sample size. During the development of the study, no data were available for PBST patients. Aerobic capacity data collected during exercise intervention studies performed on breast cancer patients were therefore utilised in the calculations. It was determined that a minimum of 16 subjects per group, and thus 32 subjects in total, would be required to detect a one standard deviation (SD) difference in aerobic capacity. A difference of one SD was considered both statistically and clinically significant.

However, the predicted identifiable subject pool of 80 was largely overestimated and consequently attaining a total of 32 subjects was not possible. This was acknowledged by the time two subjects had been recruited, completed the first two testing phases, and were close to undertaking the final testing session. Sample size calculations were reassessed based on the aerobic capacity, muscular strength, and body composition results obtained from these subjects. Due to large changes being observed as a result of the transplant and the intervention program, it was determined that only 12 subjects, 6 in each group, were required to detect a 1 SD difference, with power and significance set at 80% and 5%, respectively.

Across the 15-month recruitment and testing period, 4 patients were approached from one hospital (hospital A), while 12 were approached from the other (hospital B). All twelve patients from hospital B, were recruited into the investigation, while no patients were recruited from hospital A. Patient characteristics including the support network and living distance from the centre were potential reasons for non-participation. Additionally, the manner in which subjects were informed of the investigation was another potential factor relating to study involvement. The BMT

nurse co-ordinator at hospital A, informed patients who met the inclusion criteria, of the study by presenting them with the study's subject information letter and package. Discussion between the patient and BMT co-ordinator or treating physician regarding participation in the project was limited. By contrast, eligible patients treated at hospital B, were informed of the study by their treating physician and were strongly encouraged to participate. In summary, specific patient characteristics, and the treating physician's referral and encouragement were considered important in the recruitment of subjects.

Twelve patients diagnosed with a variety of malignancies including acute myeloid leukaemia, breast cancer, multiple myeloma, lymphoma, and rhabdomyosarcoma, were recruited between October 1997 and December 1998. Nine patients underwent one autologous PBST, while three patients underwent three consecutive transplants.

### **3.5 Autologous peripheral blood stem cell transplant procedure**

A brief description follows of the PBST protocol administered to the patients within the study. Peripheral blood stem cells were collected and cryopreserved prior to hospital admission. Shortly after admission, a high-dose chemotherapy regimen, specific to the neoplasm under treatment, was initiated. During this period, patients may have received doses of anti-nausea medicines, sedatives, diuretics, and intravenous fluids. At least 24-hours following the last chemotherapy administration, the previously cryopreserved stem cells were then transplanted. Once stem cell reinfusion had been completed, patients were able to leave the hospital, usually the following day if considered 'well', were not vomiting, had a carer and lived within thirty minutes of the hospital. However, patients were required to return daily for approximately two weeks for clinical review.

While the risk of developing oral mucositis, pharyngitis and other gastrointestinal complications is particularly high during this two week period, readmission to hospital usually only occurs when the patient experiences a high risk fever in conjunction with hypotension or tachycardia, or experiences mucositis and requires pain relief. The clinician's judgement is also a factor with regard to both hospital release and readmission. Importantly, both hospital release and readmission are

based on clinical symptoms rather than haematological counts. Generally, 60% of patients who have undergone a PBST at the recruiting hospital are readmitted. However, in contrast, 92% of the study sample required readmission.

The high-dose chemotherapy (HDC) regimen administered at the Wesley Hospital is considered to be either a 'light' or 'heavy' program. Women with breast cancer generally undertake a lighter program while all other patients undertake a heavier HDC regime. The HDC regime, usually lasting five days, was different for various diagnoses. The majority of patients with haematological malignancy received busulfan melphalan containing combinations. However, patients with Hodgkin's disease received BEAM, and the two patients with high-risk stage II breast cancer received high-dose cyclophosphamide and epirubicin with three high-dose cycles followed by stem cell support. Finally, the one patient with stage IV breast cancer, received an experimental program of thiotepa, iphosphamide and taxol for three cycles with stem cell support.

### **3.6 Exclusion criteria**

Patients experiencing specific contraindications that may have influenced safe participation in the exercise program were not eligible for inclusion into the study. The exclusion criteria were originally defined in accordance with the contraindication guidelines outlined in Winningham (1994)<sup>425</sup> and were as follows:

- white blood counts <3 000 cells/mm<sup>3</sup>
- absolute granulocyte counts <2 500 cells/mm<sup>3</sup>
- platelet counts <50 000 cells/mm<sup>3</sup>
- hemoglobin levels <10 g/dL

Patients who were diagnosed with multiple myeloma were also considered ineligible due to the risk of bone fracture. However, more patients presented with these exclusion criteria than expected, and consequently the number of potential patients for this investigation substantially declined. To enhance the ability to recruit subjects without jeopardising patient safety, the exclusion criteria were altered according to recommendations from treating physicians. This involved the inclusion of multiple myeloma patients into the study, and if patients were considered 'well' with no

clinical symptoms, participation was allowed even during periods of low blood counts, with the treating physician's approval.

### **3.7 Recruitment of subjects into experimental groups**

Once patients had received and read the subject information letter and package (Appendix IV), and noted that they were interested in participating in the study, an initial meeting was scheduled. The initial meeting provided an opportunity to obtain informed consent, all relevant patient history information and to schedule the testing phases. Depending on when the patient was informed of the study, the initial meeting was either pre- or post-transplant. For this reason, only 7 out of 12 patients entered the study at PI, while the remainder entered the study at PII.

Initially, patients were to be randomly divided into two groups, with age stratification, as they presented to the study. Unfortunately, the slow recruitment rate and low subject numbers meant randomisation was difficult. Therefore, the two groups were matched as closely as possible, by taking into account factors that had the potential to influence the level of change in an intervention project.

Two factors addressed throughout the literature that maintain the potential to influence the level of change in an intervention study are age and gender<sup>139</sup>. Previously active individuals could also potentially sustain greater benefits by maintaining exercise during treatment, when compared with previously inactive individuals initiating exercise during cancer treatment<sup>77</sup>. It therefore seemed reasonable to ensure that past exercise experience was taken into account, and that the CG and EG consisted of similar 'exercise experience' prior to undertaking a PBST and during the treatment process itself. During the initial investigator/patient interview, sufficient information was collected that allowed the level of regular exercise participation in the past ten years to be determined. The patient was categorised as 1, 2, 3 or 4 with the numbers being equivalent to no regular exercise, limited and sporadic exercise, regular exercise prior to diagnosis, and regular exercise at diagnosis and up until transplant, respectively. If the patient engaged in no planned, regular exercise program, or only recreational activity across the previous ten year period, they were allocated a 1. Exercise participation, once to

twice per week at some stage across the ten-year period was considered as being limited and sporadic. Regular exercise was considered to be participation in some form of aerobic exercise and/or resistance training, three times per week for a minimum of thirty minutes. If the patient discontinued regular exercise at diagnosis they were classified as a 3, and given regular participation was being maintained at the time of the interview, patients were allocated a 4. Other non-medical factors that were deemed potential confounding variables and therefore considered when formulating the control and exercise group, included marriage status or support network, weight at PII and living distance from the exercise centre.

Medical variables considered when devising the experimental groups included original diagnosis, the number of transplants undertaken and the treatment regimen implemented. It has been reported that the degree of rigour posed by the BMT hospitalisation experience could also influence the physical and psychosocial status of the patient<sup>14</sup>, whereby the impact of undergoing a BMT would be less for those patients who experienced fewer post-BMT complications. For this reason, patients were not allocated a group until PII had been completed.

Table 3.1 summarises the characteristics of the two groups. While certain variables such as the mean age, weight at PII and living distance from the centre appear different between the two groups, these differences were not statistically significant ( $p=0.052$ ,  $0.466$ , and  $0.209$ , respectively). Additionally, the investigator tried to ensure that both the statistical mean and range were similar for all factors, between the two groups. For example, both groups contained a 64-year-old male, and both groups contained a patient who lived in close proximity to the centre (within 10kms) and a patient who lived more than an hours drive from the centre (100kms). Finally, with respect to the prognosis of the patients under investigation, it was previously found that 50-80% of patients undertaking a PBST would become a long-term survivor<sup>166</sup>. By comparison, at the time of completion of this thesis, 4 patients in total (2 control and 2 exercise group participants) had died. The control group participants had been diagnosed with multiple myeloma and non-Hodgkin's lymphoma, while the exercise participants had been diagnosed with rhabdomyosarcoma and non-Hodgkin's lymphoma.

**Table 3.1** Group characteristics

Variable	Control Group	Exercise Group
Age (years)	Mean = 54.5 Median = 54 Range = 46 – 64	Mean = 39.5 Median = 40.5 Range = 16 – 64
Gender	4 males 2 females	3 males 3 females
Marriage status	Married/significant relationship = all 6 patients	Married/significant relationship = 5 out of 6 Single = 1 out of 6
Previous exercise history *	1 = 1 patient 2 = 3 patients 3 = 1 patient 4 = 1 patient	1 = 1 patient 2 = 3 patients 3 = 1 patient 4 = 1 patient
Weight at PII	Mean = 71.82kg SD = 23.71kg Range = 62.9kg	Mean = 87.35kg SD = 26.09kg Range = 68.8kg
Living distance from the centre	Mean = 80km Range = 10 – 150km	Mean = 33km Range = 5 – 100km
Diagnosis	1 x acute myeloid leukaemia 1 x high risk stage II breast cancer (BC) 2 x multiple myeloma 1 x non-Hodgkin's lymphoma (NHL) 1 x stage IV BC	1 x lymphoblastic lymphoma/leukaemia 1 x high risk stage II BC 1 x rhabdomyosarcoma 3 x NHL
Number of transplants	1 transplant = 4 patients 3 transplants = 2 patients	1 transplant = 5 patients 3 transplants = 1 patient
High dose chemotherapy regime (HDC)	'Lighter' program = 2 patients 'Heavy' program = 4 patients	'Lighter' program = 1 patient 'Heavy' program = 5 patients

\* 1, 2, 3 or 4 is equivalent to no regular exercise, limited and sporadic exercise, regular exercise prior to diagnosis, regular at diagnosis and up until transplant, respectively.

### 3.8 Testing phases

This investigation consisted of three primary testing phases, PI, PII and PIII, and two additional testing phases, I1 and I2, for the immunological parameters assessed. Phase I was scheduled as close as possible prior to the transplant. As noted in Chapter 2, patients are at risk of a decline in functional capacity and quality of life during the period between diagnosis and treatment cessation. This investigation aimed to assess the impact of a PBST and it was therefore essential to ensure that the

data collected was reflective of the impact of a PBST, and not other factors that might have occurred prior to the transplant. For the seven patients recruited pre-transplant, PI was scheduled between one to three days prior to the start of high-dose chemotherapy.

It was crucial that PII be implemented as close as possible to treatment cessation/stem cell reinfusion. However, as previously noted, while some patients undertook one transplant, others were required to undergo three transplants, and others still were required to undertake RT following transplantation (three patients, one in the control group, and two in the exercise group). Due to the diversity of the treatment regimens present within the group investigated, PII was standardised as the number of days following treatment cessation. Day of treatment cessation (day 0) was classified as the day of stem cell infusion (for those undertaking three transplants, this reflects the day of stem cell infusion of the last transplant) or the final day of RT. Patients were usually discharged from hospital either on the day stem cells were reinfused or the following day. However, within 1-2 weeks following stem cell infusion, 92% of the study sample were readmitted into hospital for an additional 1-2 weeks due to post-transplant complications, such as the development of a fever. Phase II was scheduled as close as possible to discharge from hospital and occurred with a range of 17-21 days following treatment - day '0'. Testing PII then became the reference point for the consecutive testing phases with I1, I2 and PIII scheduled at approximately one-month, two-months, and three-months following PII. Table 3.2 summarises the timing of medical events and testing phases.

**Table 3.2** Timing of medical events and testing phases

Medical Events and Testing Phases	Mean	SD	CV	Range
PI (no. of days before the start of HDC)	-8.43	-0.98	11.6%	-7 to -10
HDC duration (number of days)	4.67	0.78	16.7%	3 to 5
Day of stem cell infusion	0	0		0
Day of hospital discharge (no. of days from stem cell infusion)	1	0.6	60%	0 to 2
PII (no. of days from stem cell infusion)	17.08	2.64	15.5%	+14 to +21
I1 (no. days from phase II)	29.67	1.56	5.3%	28 to 32
I2 (no. days from phase II)	56.75	2.09	3.7%	54 to 60
PIII (no. days from phase II)	85	2.26	2.7%	82 to 89

### **3.9 Experimental groups**

Patients entered the study at either PI or PII. During these first two testing phases, the effect of the transplant was being assessed and all patients were considered to be in the same group (SG). Immediately after PII, patients were allocated to either the control/stretching group (CG) or the exercise intervention group (EG).

#### **3.9.1 The intervention program**

**Control group:** An adequate control group is required to ensure that changes observed are a result of the intervention, and not confounding variables such as ‘investigator attention’ or ‘patient interaction and support’. In order to ensure that these variables did not become confounding factors, investigator/patient contact and patient/patient contact was standardised across the intervention period between the CG and EG. To ensure the patients allocated to the CG maintained a level of enthusiasm and expectation for results, a stretching program was implemented.

While participation in the stretching program could potentially lead to mobility improvements, it was unlikely that the program would lead to significant improvements in the physiological variables being assessed. The stretching program was implemented three times per week, within the patient’s home environment. The variables of the program are outlined in Table 3.3. The investigator travelled to the patient’s home either once or twice per week, which meant that the patient performed the stretching program unsupervised, once-twice per week. At least one telephone call was implemented during the weeks where the investigator could only visit the patient’s home on one occasion. Progression of the stretching program was achieved by increasing the total number of stretches performed within each session and by holding each stretch for a longer period.

**Exercise group:** The intervention implemented in the EG consisted of a three-month duration, moderate intensity, mixed type (aerobic and resistance training) exercise program.

**Aerobic program:** Patients were required to participate in aerobic exercise, three times per week. At least two out of three of these sessions were performed on a treadmill and cycle ergometer at the Queensland University of Technology (QUT) Human Movement Studies Clinic, Brisbane. The third session was unsupervised and could be any form of aerobic exercise, as long as the participants met the required intensity and duration. Patients chose walking, jogging, cycling or swimming during their unsupervised sessions.

The intensity of each session at the centre was regulated via the assessment of HR and RPE. During the first four weeks of the twelve week program, exercise intensity was measured via the use of Polar™ HR monitors, worn continuously during the sessions, in conjunction with regular use of the revised Borg RPE scale<sup>3</sup>. During subsequent weeks, the use of the HR monitors declined and RPE scale increased. Reducing reliance on the HR monitors for assessing intensity throughout the sessions was deemed important to ensure that patients could successfully exercise at an appropriate intensity in an unsupervised setting, without the need for equipment. All unsupervised sessions were assessed via the RPE method.

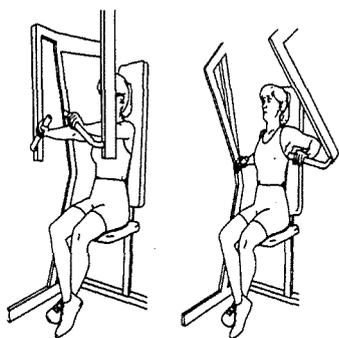
Progression was achieved through a combination of intensity and duration. The program was initiated at an intensity represented by 70% of the calculated maximum HR, for a total exercise duration of twenty minutes. This was twenty minutes of total exercise time, which meant for those patients whose function was at the lower end of the range, rest periods between shorter bouts of exercise (two to five minutes) were required. By the end of the three-month period, patients were working at an intensity between 70-90% of calculated HRmax for a total exercise duration of forty minutes. There were no restrictions placed on the patients with regard to whether exercise was of a continuous duration, or divided into several bouts with rest periods or the resistance program between bouts.

**Resistance program:** Side effects from cancer and treatment may lead to limitations in neuromuscular coordination which may be exacerbated by fatigue. For this reason, during the initial phases of the program, patients were required to perform all resistance training with the use of weight training machines. Following the first six to eight weeks of training, two free weight exercises were introduced.

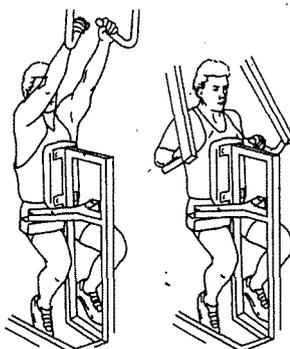
The initial weight program consisted of a 'seated bench press', 'lat pulldown' and 'leg press' (as shown by Figure 3.2a, b & c, respectively). These three exercises were chosen as they utilise most of the major upper and lower body muscle groups including the pectorals, latissimus dorsi, deltoids, rhomboids, triceps, biceps, quadriceps, gluteal, hamstring and calf muscles.

**Figure 3.2** Initial resistance exercises

**(a) Seated bench press**



**(b) Lat pulldown**



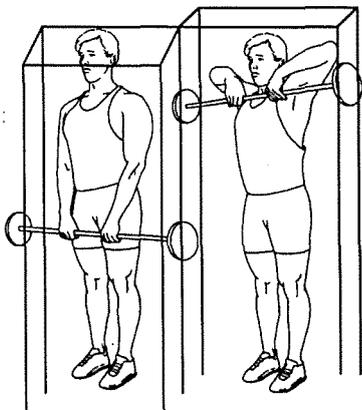
**(c) Leg press**



As familiarity improved and patients progressed, an 'upright row' (Figure 3.3a) using a 'Smith machine', was introduced, usually within the fifth to sixth week of the program. Lastly, by week eight, the 'seated shoulder press' (Figure 3.3b) and 'lunges' (Figure 3.3c), using free weights were introduced.

**Figure 3.3** Resistance exercises progressively introduced

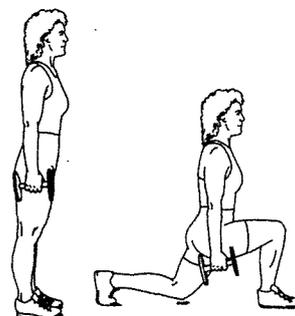
**(a) Upright row**



**(b) Seated shoulder press**



**(c) Lunges**



Verbal instructions and practical demonstrations were given on how to use each piece of equipment, the correct body posture required, and the appropriate breathing technique. Each exercise was implemented throughout a full range of motion and was undertaken at a slow pace, to the count of three for the lifting and lowering motion. Patients were required to undertake two resistance training sessions per week, at the QUT, Human Movement Studies Clinic. A minimum of 48-hours rest was required between each session. This rest simply applies to the performance of resistance training and thus the patient was able to participate in aerobic exercise during this period.

The number of repetitions performed to fatigue is an important consideration when designing a strength program and should reflect the goal of the program. Greater strength gains are yielded when repetitions of 4-6 repetition maximum (RM) are applied. By increasing the repetition range to 12-20RM, muscular endurance will be favoured. The term 'high-intensity' programs are usually applied to strength programs utilising a 1-6RM, and 'moderate-intensity' programs are generally considered as those implementing an 8-15RM program<sup>117</sup>. While improvement in muscular strength was a primary aim for this population, other factors such as weight training experience, risk of injury, and blood counts were also considered when deciding an appropriate repetition range for the population investigated.

The resistance program was progressed in a number of ways. Firstly, the number of exercises performed during each session increased from three to six across the three-month period. Secondly, for the initial six weeks, repetitions were set at 15-20, and the weight was set at a level which induced failure between this repetition range. Failure was determined as the time when the patient was unable to perform the movement through full range of motion with correct body posture. During weeks 7-12, the repetition range was lowered (8-12 repetitions) and the weight lifted was increased (weight lifted ensured 'failure' between the designated repetition range).

While three sets of 8-12 repetitions performed three times per week is a typical prescription for many strength programs, the optimal number of sets required per exercise session remains controversial<sup>117</sup>. However, the existing literature demonstrates that single set programs are as equally effective as multiple set

programs when aiming for strength gains in an untrained population. In addition, the amount of time required to perform a single set program is considerably less than a multi-set program<sup>117</sup>. Another factor to consider when prescribing weight training, is the frequency of the sessions. The literature suggests that when prescribing for ‘beginners’, a minimum of two days per week is appropriate as it allows time for recuperation and produces similar benefits when compared with more frequent programs<sup>117</sup>. Therefore, it was determined that only one set of each exercise, two times per week would be performed throughout the duration of the program. The intervention characteristics for both the CG and EG are reported in table 3.3.

**Table 3.3** Intervention variables for the control and exercise group

CG	EG	
Stretching program	Aerobic exercise program	Resistance exercise program
<b>F</b> = 3 x wk 1 <sup>st</sup> 4 wks: 20 stretches 2 <sup>nd</sup> 4 wks: 25 stretches 3 <sup>rd</sup> 4 wks: 30 stretches ➤ Each stretch was performed twice ➤ Stretches were performed for all major muscle groups each session ➤ Stretches were taken to the point of discomfort, not pain ➤ Stretches were held for 15-30 seconds	<b>F</b> = 3 x wk <b>I</b> = 70 – 90% of HRmax <b>T</b> = 20 – 40 minutes	<b>F</b> = 2 x wk <b>Sets</b> = 1 <b>Wt</b> = to failure <b>Reps</b> = 1 <sup>st</sup> 6 wks: 15-20 2 <sup>nd</sup> 6 wks: 8-12

\* **F** = frequency, **I** = intensity, **T** = duration, **Wt** = weight, **Reps** = repetitions

### 3.10 Statistical analysis of data

Physiological and quality of life data were collected at PI, PII, and PIII. However, data were also collected at I1 and I2 for immunological measures. Prior to statistical analysis, data were tested for normal distribution and were considered ‘normally distributed’ when all of the following criteria were met:

- the mean lies within 10% of the median
- the SD is no more than 50% of the mean
- the skewness CE lies between -3 and +3
- the kurtosis CE lies between -3 and +3

When the data did not meet these criteria, the results were log-transformed, and then re-tested for normal distribution. Statistical procedures were applied either on 'normally distributed' original or log-transformed data, and the level of significance was set at 5% (two-tailed). Table 3.4 represents the data set, which were dealt with during the statistical analysis of body composition, aerobic capacity, muscular strength, bone turnover and quality of life measures.

**Table 3.4** Representation of the data set commonly dealt with during statistical analysis

Group		Testing phases			
		PI	PII	PIII	
Study Group (SG)	Control Group (CG)				
	Subject	1	x	x	x
		2	MD	x	x
		3	MD	x	x
		4	x	x	x
		5	x	x	MD
		6	MD	x	x
		n	3	6	5
	Exercise Group (EG)				
	Subject	1	x	x	x
		2	MD	x	x
		3	x	x	x
		4	x	x	x
		5	MD	x	x
		6	x	x	x
	n	4	6	6	
	n (SG)	7	12	11	

MD = missing data

x = data point

In order to answer the questions raised by the thesis, a number of comparisons were required:

- between PI and PII data of the SG;
- between PI and PII, PII and PIII, PI and PIII data of the CG and EG; and
- between PIII of the CG and the EG.

Multiple simple t-tests were inappropriate due to the risk of increasing the presence of a Type I error. Therefore, a 2-way repeated-measures analysis of variance (RM-

ANOVA) was used to determine the group by phase interaction (exercise by time). As a consequence of the repeated measures data set being incomplete (that is  $n=7$ , 12 and 11 at PI, PII and PIII, respectively) a random effects mixed model (REMM) was applied. Unlike the standard approach of a 2-way RM-ANOVA, the REMM was able to accommodate the partially incomplete records and relatively small sample size, while maximising power<sup>183</sup>. As a factor of the model specifications, subjects were treated as random effects. Furthermore, simple contrasts were defined and tested within the model. Therefore, the following information was derived via the use of the REMM:

- mean and standard errors for each of the testing phases (PI, PII, I1, I2 and PIII) for each group (SG, CG and EG);
- testing phase contrasts – comparisons between PI and PII, PI and PIII, and PII and PIII for the SG, CG and EG; and
- group contrasts – comparisons between PI, PII and PIII measures of the CG and EG. During these comparisons, the model accounted for baseline measures of the variable under investigation.

Although only 4 subjects were used to assess energy expenditure changes across the testing phases, the data were analysed in the same manner as previously described. Additionally, the assessment of immunological changes across time, required 2 additional testing phases. Again, these data were analysed via the use of the REMM. Therefore, the REMM approach has been applied during data analysis throughout Chapters 4-9. Any other statistical methods used to analyse data have been outlined in the relevant chapters.

The standard 2-way RM-ANOVA was also applied to the physiological and QoL data measured, and as such restricted the analysis to cases with data available at all testing phases (2 control subjects and 4 exercising subjects). As a consequence of the reduced sample size, statistical power decreased and no statistical differences were detected in the analysis of all functional capacity and quality of life measures. However, the trend of change between pre- and post-transplant, and pre- and post-intervention period were similar to that observed via the use of the REMM, lending support for the use of the latter model.

# CHAPTER FOUR

## STUDY ONE

### **Changes in energy expenditure and body composition following a PBST and participation in an exercise program**

*“Eating alone, will not keep a man well; he must also take exercise. For Food and exercise, while possessing opposite qualities, yet work together to produce health” Hippocrates in McGinnis (1992)<sup>242</sup>*

**List of abbreviations specific to Chapter four**

ALL	Acute lymphoblastic leukaemia
BW	Body weight
CG	Control group
EI	Energy intake
EG	Exercise group
FFM	Fat free mass
FM	Fat mass
%BF	Percentage body fat
PBST	Peripheral blood stem cell transplant
PI	Phase I
PII	Phase II
PIII	Phase III
REE	Resting energy expenditure
SG	Study group
TEE	Total energy expenditure
TEF	Thermogenesis of food
VO <sub>2</sub> max	Maximal aerobic capacity

## 4. Changes in energy expenditure and body composition following a PBST and participation in an exercise program

---

### 4.0 Introduction

It is well recognised that if total energy expenditure (TEE) exceeds energy intake (EI), a reduction in body weight will result. A decrease in body weight following treatment for cancer is a common side effect<sup>170</sup>, particularly for patients undergoing a PBST. Elevated metabolic demands and impaired protein-sparing mechanisms, in conjunction with reduced energy intake, inactivity, and specific chemotherapeutic and steroid treatment regimens may be contributing reasons for the negative energy balance observed in some cancer patients<sup>67, 115</sup>. Furthermore, changes in the energy balance and body composition of a patient have the potential to impose deleterious effects on functional capacity.

Since conventional medicine has failed to improve body composition following treatment, it is important to examine other intervention strategies known to influence both EE and body composition. Exercise is one such intervention strategy. However, a primary concern for patients, health professionals and carers might be that increasing participation in physical activity may lead to an exacerbation of the patient's weight reduction. It is important to note that these concerns may be contributing to the common advice offered to patients such as 'take it easy' and 'get plenty of rest'. Evidence providing support for the use of exercise in correcting an energy imbalance and body composition is required to alter this notion.

#### 4.0.1 Purpose

Objective 1: To investigate changes between pre- and post-PBST measures of TEE and body composition.

*Research hypothesis for objective 1:*

Total energy expenditure will be elevated and body composition will be adversely affected following a PBST (as determined by pre- and post-transplant measures).

Objective 2: To investigate the role of a three-month duration, moderate intensity, mixed type exercise program on TEE and body composition, post-PBST.

*Research hypothesis for objective 2:*

Participation in the exercise program will lead to an increase in TEE. Additionally, the exercising patients will experience an improvement in body composition, specifically an increase in functional tissue, during this same period.

## 4.1 Literature Review

The energy balance equation states that energy intake is equivalent to energy expended and energy stored<sup>410</sup>. “Human accommodation and adaptation to changes in energy intake have been an area of controversy for decades”<sup>340</sup>. While it is well established that EE alters with changes in intake, there is inconsistency in the available data with regards to the magnitude of such change. Another controversial issue is how EE alters to accommodate for additional energy requirements during such periods as pregnancy, lactation and growth<sup>340</sup>. While this investigation will review the literature with regards to both sides of the energy equation, of primary importance to this investigation are the changes observed in TEE.

### 4.1.1 Total energy expenditure

Total energy expenditure (TEE) is comprised of resting energy expenditure (REE), thermogenesis, physical activity and the energy cost of growth<sup>88</sup>. Due to the age of the subjects in this investigation, the energy cost of growth is considered negligible and therefore only REE, thermogenesis and the energy cost of physical activity will be discussed. Sixty to seventy per cent of TEE is explained by resting metabolic rate<sup>62</sup> or REE, while approximately 10% or less of TEE can be explained by the thermogenic effect of food<sup>201,340</sup>.

An experimental variation in TEE of 8.5% under sedentary and controlled living conditions and 12% under free-living conditions has been suggested by reliability studies<sup>142</sup>. Resting metabolic rate, body composition, gender, age, pregnancy and particular disease states can contribute to variations in TEE. It has been cautioned that this variation should be considered when undertaking interventional studies and when attempting to compare TEE between subjects or other investigations<sup>142</sup>.

TEE has been described as ‘quite robust’, as it remains relatively stable when challenged by external stimuli such as excess energy intake, exercise intervention and some diseased and stressed states<sup>142</sup>. The lack of net change in TEE is often a consequence of counteracting effects whereby one component of TEE is elevated while another is reduced<sup>142</sup>. Nevertheless, in many conditions including cancer, an

energy imbalance is evident through significant weight changes. For this reason it is important to begin to investigate changes in EE in order to understand the etiology of this energy imbalance. Unfortunately, while investigations assessing REE changes within the cancer population could be identified, few were found that calculated TEE<sup>177</sup>.

In a study of premenopausal and perimenopausal women with breast cancer, REE was assessed via indirect calorimetry, while the average daily EE was estimated on the basis of self-reports using a structured physical activity diary. The assessments quantified changes between the pre- and post-treatment period (women were either treated with radiation or chemotherapy)<sup>201</sup>. Resting energy expenditure, expressed as kilocalories per kilogram lean body mass per day, increased significantly between the pre- and post-treatment period, as did TEE and EE from physical activity. However, the increases in the latter two variables were slight and insignificant. In contrast, it was identified in a non-small cell lung cancer patient group that TEE was reduced when compared with age- and sex-matched controls. The researchers reported that while REE increased in these patients, physical activity levels demonstrated a corresponding decline, and taken together these changes led to a reduction in TEE<sup>177</sup>.

Another investigation assessed both the TEE and patterns of physical activity in survivors of childhood malignancy<sup>410</sup>. Children treated for acute lymphoblastic leukaemia (ALL) maintained a reduced TEE when compared with healthy sibling controls and other children treated for a variety of malignancies. The reduction in TEE was explained by reduced patterns of physical activity, whereby energy expended above basal metabolic rate declined.

Obviously, more work quantifying changes in TEE in cancer patients is required before any conclusions can be made with regard to the effect of treatment on TEE. Further, the studies outlined above used relatively unreliable techniques to assess TEE, with none using the more accurate doubly-labelled water method. It seems plausible that the use of this technique in the area has the potential to provide more definitive results.

#### 4.1.1.1 Resting energy expenditure

Sleeping metabolic rate and the energy cost of arousal comprises REE, which can be defined as the minimum rate of energy expended in an awake, relaxed individual, resting on a bed, following an overnight fast<sup>314</sup>.

While REE is elevated in many cancer patients, this observation has not been consistent<sup>331</sup> and may be dependent on tumour types<sup>50</sup>. Sakurai and Klein (1998)<sup>331</sup> reviewed eleven investigations that assessed changes in REE as a result of treatment in a variety of patients diagnosed with gastrointestinal, gynaecological, genitourinary, colorectal, stomach, bronchial, sarcoma, esophageal, and metastatic cancer. Normal, elevated and decreased REE states were reported by these investigations. Two of the eleven studies were undertaken on greater than 150 patients, and both studies found patients experiencing hypo-, normo- and hyper-metabolic states. Unfortunately, the majority of the studies reviewed failed to control for factors that have the potential to influence REE such as dietary intake, nutritional status, infection, fever, and recent cancer therapy<sup>331</sup>. Additionally, few studies measuring REE have adequately accounted for changes in body composition. An increase in the mass of vital organs relative to total fat free mass (FFM) has the capacity to produce alterations in TEE which appear as hypermetabolism, but which are in fact independent of changes in the metabolic activity per unit weight of tissue<sup>178</sup>.

Inconsistent findings have been found by others, not reviewed by Sakurai and Klein (1998)<sup>331</sup>. No change in REE was observed in gastrointestinal cancer patients when compared with controls<sup>420</sup>. In contrast, patients being treated for breast cancer showed an increase in REE<sup>201</sup>. While the increase in REE expressed per kg of FFM was related in part to the decreased FFM observed during the same period, the overall REE (kcal/day) increase was unexpected and could not be explained by available data. Newly diagnosed lung cancer patients also demonstrated a disturbance in energy balance, which included an elevation in REE (>110% of predicted)<sup>372</sup>. Inflammation and central tumour localisation reflected by C-reactive protein values were found as contributing factors to this elevation. Similar findings were found in unresectable pancreatic cancer patients. These patients showed a

significant increase in REE compared with controls when expressed in relation to total body weight (>33%), FFM (>28%) or body cell mass (BCM) (>37%)<sup>115</sup>.

An elevated REE was also observed in hypermetabolic non-small cell lung carcinoma patients<sup>123</sup>. However, this returned to normal within three months of curative surgery. Those patients characterised with normal metabolism showed no REE change following surgery, as did those patients with tumour recurrence. A further investigation performed on small cell lung cancer patients noted while hypermetabolism was found, it was considered small, and that a reduction of tumour mass results in a reduction in REE<sup>178</sup>. These findings lend support to the hypothesis that tumours have the potential to elevate basal metabolic rate.

*In vitro* studies reported by Jebb et al (1994)<sup>178</sup> suggest that the oxygen consumption of human tumour cells is comparable with that of organs such as the liver, kidney and brain. Given this theory, the rise in REE observed in cancer patients cannot be explained by the tumour alone, and therefore the energy expended from other body tissues must also rise. Several theories have been proposed for the mechanism of elevated EE in other tissues and include a disordered substrate cycle, an elevation in Cori cycle activity, a rise in protein turnover or the effect of tumour-derived proteins<sup>178</sup>. All theories may contribute to the rise and given the magnitude of change in REE, the ability to dissect its individual compartments may be difficult<sup>178</sup>, if not impossible. Another unclear issue proposed was how the increase in REE related to TEE. It seems possible that the energy expended on physical activity and the thermogenesis of food (TEF) may alter to stabilise TEE<sup>178</sup>.

#### 4.1.1.2 Energy intake and thermogenesis of food

Limited data are available that directly assess the energy cost of thermogenesis in cancer patients. Many studies maintain the assumption that approximately 10% of TEE is spent on TEF, with TEF being influenced by food, thermogenic agents (caffeine or nicotine), exposure to cold and emotional arousal<sup>96</sup>. However, this assumption may be violated due to the adverse effects that symptoms commonly experienced by cancer patients such as nausea, vomiting and pain, have on appetite and food intake. Many chemotherapeutic agents, including dactinomycin,

bleomycin, cyclophosphamide, 5-fluorouracil, methotrexate and vincristine, all have the potential to reduce food intake by causing constipation, nausea, vomiting, diarrhea, dry mouth and mouth sores<sup>67</sup>. Patients who have received high-dose CT or RT, such as PBST patients, are at a particularly high risk of experiencing these symptoms<sup>68</sup>. Although supportive care is continually improving the control of such symptoms<sup>178</sup>, some patients still find it difficult, if not impossible to consume food<sup>68</sup>.

In the one study identified that assessed TEF, a reduced thermogenesis of food was reported in weight-losing gastrointestinal cancer patients<sup>420</sup>. It was suggested that the decline in diet-induced thermogenesis was an element of starvation adaptation, subsequent to weight loss, and that the weight loss seen in cancer cachexia is not caused by altered thermogenesis.

While energy intake is an important determinant of overall energy balance<sup>178</sup>, it is also a crucial factor in TEF. Therefore investigations reporting energy intake data can lend some information to changes in this component of EE. Responses (978 out of 1667) to a 'health behaviour and readiness to pursue life-style changes' questionnaire showed that 55% of cancer respondents ate fewer than five daily servings of fruit and vegetables<sup>95</sup>. Prostate carcinoma patients reported eating significantly fewer servings when compared with breast carcinoma patients ( $p < 0.001$ ). A study performed on breast cancer patients indicated that energy intake significantly decreased across the course of a treatment regimen, was 'erratic' and appeared to be responsive to the timing of treatment<sup>94</sup>. Finally, in relation to children undergoing a BMT, suboptimal nutritional support and the need for intravenous fluids (usually at the expense of nutrition) were given as potential reasons for basal energy requirements barely being met. Importantly, others have found that although weight-losing patients exhibit a reduction in food intake per kilogram of their usual weight, when current weight is taken into account, food intake per kilogram of body weight does not fall<sup>150</sup>.

In contrast to weight-losing cancer patients, certain types of cancer, in particular breast cancer, make weight gain more likely. While length of treatment, type of treatment, menopausal status, and alterations in physical activity levels are all potential causes of this observed weight gain, an increase in energy intake is

regarded as the most likely cause<sup>96</sup>. However, an increase in energy intake is not a consistent finding in women being treated for breast cancer<sup>201</sup> and it is therefore inappropriate to state that energy intake is the primary cause of weight gain.

Patients have been recommended to increase their energy intake during treatment with the aim of maintaining an energy balance<sup>50</sup>. Protein intake recommendations range from 1.5g/kg/day to 2.5g/kg/day, and increase further when surgery, radiation or chemotherapy treatment is present<sup>50</sup>. Obviously the need to increase EI during treatment will be dependent on EE. It is difficult to support recommendations for an increase in EI, when findings relating to changes in EE following cancer diagnosis and treatment remain inconsistent.

#### **4.1.1.3 Physical activity**

Anecdotally, habitual levels of activity appear to reduce in 'sick' patients<sup>177</sup>. A recent review of the literature on physical activity in women with breast cancer noted that while few carefully conducted studies were found, decreasing levels of physical activity were reported, and were associated by some with the gain in weight often observed in these patients<sup>201</sup>. Others have found an increase in the energy expended during physical activity in premenopausal and perimenopausal patients with breast cancer, between the pre- and post-treatment period<sup>201</sup>. The increase observed however, was not significant and the results should be considered with caution due to the lack of measurement undertaken prior to surgery and during treatment. Declines in physical activity levels have also been identified in non-small cell lung cancer patients<sup>177</sup>. It was suggested that this was a spontaneous decline to counterbalance an elevation in REE. However, a reduction in muscle mass, and therefore potentially functional capacity, is associated with decreased activity levels<sup>209</sup> and thus it should not be considered as an appropriate means of balancing the energy equation.

While investigations have evaluated changes in physical activity levels in response to treatment periods, it is also necessary to determine the longer-term changes. One such study assessed the TEE and patterns of physical activity in a group of children who were considered as being in remission from childhood malignancy, for a minimum period of eighteen months. The study demonstrated that children treated

for ALL maintained reduced patterns of physical activity when compared with healthy sibling controls and other children treated for a variety of malignancies<sup>410</sup>.

Although evidence is limited, it is sufficient to conclude that energy expended on physical activity predominantly decreases following cancer diagnosis and treatment. As mentioned earlier, since participation in physical activity is associated with an increase in energy expended, health care providers and carers may find it difficult to recommend participation in physical activity post-treatment, particularly for weight-losing patients. However, these fears may be unfounded and it is crucial to begin to investigate how the energy balance is influenced through the integration of exercise post-treatment. Unfortunately, no investigations could be found that addressed this issue in the cancer population and only limited data can be drawn upon from other population studies for recommendations.

Total energy expenditure increased by 12%, in young obese boys following four weeks of aerobic training at an intensity of 50-60%  $\text{VO}_2 \text{ max}$ <sup>37</sup>. In contrast, while resting metabolic rate and EE associated with exercise training increased in a study of healthy elderly persons, TEE showed no significant elevation<sup>143</sup>. The observation was explained by a compensatory reduction in physical activity related energy expenditure during the remainder of the day. This counterbalancing reduction in energy expended performing 'daily activities', to the increase in EE spent performing physical activity, is not an ideal response in cancer patients, since the primary goal of an exercise intervention would be to improve the ability to perform daily activities. Extensive research is required in the cancer population to determine the effect of exercise on energy balance.

#### **4.1.2 Impact of cancer treatment on body weight and body composition**

Weight change is a common side effect following cancer and may be dependent on the cancer type, stage or treatment<sup>50</sup>. A positive imbalance between energy intake and expenditure leads to the storage of accumulated energy as excess body fat<sup>411</sup>, in most cases. This imbalance is a result of either excessive energy intake or reduced or impaired energy expenditure, or a combination of both. Alternatively, metabolic

disturbances and an energy intake too low to meet metabolic requirements can lead to weight loss<sup>362</sup>.

Cancer cachexia, or progressive loss of body weight, protein and lipid stores, and body cell mass (BCM), is a common involuntary symptom of cancer patients<sup>115, 170, 177, 331, 437</sup>. The word cachexia simply means 'bad condition' and is used to describe any disease that results in host tissue wasting<sup>390</sup>. Inui (1999)<sup>170</sup> reported literature statistics illustrating that approximately half of all cancer patients demonstrate a syndrome of cachexia, characterised by adipose tissue and muscle mass loss. Cachexia tends to become more pronounced with disease progression, and solid tumour patients seem to be at a greater risk, as are children and the elderly. Given that the percentage of patients experiencing weight loss varies amongst cancer types, it seems evident that some tumours predispose cachexia more than others, with gastrointestinal cancer being associated with the most marked weight loss<sup>177, 390</sup>. It should be remembered that weight loss is a statistically significant predictor of survival, independent of tumour type and stage, and performance status, and thus cancer cachexia is clinically important<sup>99</sup>.

Cancer cachexia has previously been classified as consisting of three stages:

- preclinical, during which there are abnormal acid and lipid profiles, however, the patient does not exhibit any clinical signs of the condition;
- hypermetabolic, whereby patients begin to exhibit lethargy and early weight loss signs; and
- hypometabolic, where metabolic rate is below normal and energy intake is diminished. This final stage is also associated with marked debilitation, weakness and biochemical evidence of a negative nitrogen balance<sup>67, 274</sup>.

Although the etiology of cachexia is not certain, a reduction in food intake during tumour growth, an EE imbalance and other metabolic alterations are attributed to this weight loss<sup>67, 115, 379</sup>. A direct effect of the tumour, or potentially the secretion of humoral factors including cytokines, hormones or other mediators, may also act to induce hypermetabolism<sup>178</sup>.

Changes in carbohydrate, lipid and protein metabolism have been documented in tumour-bearing hosts, with cancer cachexia being characterised by a shift in nutrient use to immune response and disease resistant processes, rather than muscle growth and maintenance<sup>135</sup>. Typically BCM, body fat and FFM are reduced, and the extracellular-intracellular water ratio is altered in cachexia cancer patients<sup>357, 381</sup>. BCM is of great importance, since it comprises the body compartment containing most of the tissues vital to normal functioning and thus accounts for 95% of the body's metabolic activity<sup>327, 362</sup>. While patients may survive a body weight loss of up to 50%, a 30% loss in body weight is almost always fatal<sup>390</sup>.

Tisdale (1997)<sup>390</sup> reported evidence suggesting that unlike starvation, where more than 75% of weight is attributed to body fat loss, the weight loss in cancer patients arises equally from muscle and fat loss. This evidence was further supported by others noting that "cancer cachexia may be characterised by a disproportionate loss of lean tissue, suggesting a failure of the normal regulatory processes which conserve skeletal muscle and visceral organs during periods of undernutrition, uncomplicated by disease"<sup>177</sup>. However, this is not a general consensus as others have reported that fat loss still accounts for the majority of weight loss occurring in cancer cachexia<sup>274</sup>. While there is consistent evidence in the HIV population demonstrating a disproportionate loss of lean tissue and relative sparing of fat with loss of body weight<sup>252</sup>, evidence has also indicated that the baseline fat content determines the level of fat loss. That is, those who begin with a greater fat mass will lose a higher level of fat, in comparison to a significantly greater proportion of lean body mass loss in those who have a baseline fat content of less than 15%. As the energy balance becomes more negative, the proportion of weight lost as lean body mass increases.

In relation to cancer patients, it has been noted that depletion of skeletal muscle exceeds that of visceral mass in cancer cachexia<sup>390</sup>. Theories have been proposed suggesting that a tumour/host competition for nutrients exists, with the aggressive tumour succeeding at the expense of the host. However, some patients with large tumours show no signs of cachexia, while others with relatively small tumours exhibit significant cachexia, making these theories unlikely<sup>390</sup>.

Carbohydrate, fat and muscle metabolism abnormalities have also been reported in cancer patients<sup>274, 390</sup>. The production of lactic acid associated with some tumours leads to an elevation in the conversion of lactate to glucose by the liver. This is an energy-consuming process and studies have found a correlation between increased Cori cycle activity and weight loss. These findings have been supported in animal investigations reported by Ogilvie (1998)<sup>274</sup>. Tumours preferentially metabolise glucose for energy by anaerobic glycolysis forming lactate as an end product. Therefore, energy is required to convert lactate to glucose via the Cori cycle, resulting in a net energy gain by the tumour, and a corresponding energy loss by the host.

Given that fat loss accounts for a substantial proportion of weight loss, it is not surprising that cancer patients experience lipid metabolism abnormalities<sup>274</sup>. An increased glycerol and fatty acid turnover has been observed in some cancer patients when compared with healthy subjects<sup>390</sup>. Ogilvie (1998)<sup>274</sup> reported evidence demonstrating that the increased levels of free fatty acids, very low density lipoproteins, triglycerides, plasma lipoproteins and hormone-dependent lipoprotein lipase activity, and decreased levels of endothelial-derived lipoprotein lipase, are a result of the decreased lipogenesis and increased lipolysis observed in cancer patients.

Decreased muscle mass, reduced skeletal protein synthesis and altered nitrogen balance in conjunction with concurrent elevations in skeletal protein breakdown, liver protein synthesis and whole body protein synthesis have also been shown in studies with cancer patients<sup>274, 390</sup>. Tumours preferentially utilise protein for energy, and certain amino acids for gluconeogenesis, unfortunately at the expense of the host. Additionally, total skeletal muscle mass decreases during cachexia have been shown, and white or phasic muscle experiences faster losses when compared with red or tonic muscles<sup>390</sup>. Increased muscle catabolism, decreased protein synthesis or a combination of the two, may contribute to the peripheral muscle wasting observed in some cancer patients<sup>252, 390</sup>. The use of amino acids for energy by the tumour becomes clinically important when protein synthesis is exceeded by the loss. At this time, immune response, gastrointestinal function and wound healing are some of the bodily functions adversely influenced<sup>274</sup>.

Thirty per cent of newly-diagnosed lung cancer patients studied demonstrated a weight loss of 10% or more from their preillness stable weight<sup>372</sup>. A combination of elevated REE and reduced dietary intake were reasons given for the weight loss. An investigation on patients with pancreatic cancer showed that on average patients had lost 18% of their preillness weight with part of this loss being reflected by significant reductions in FFM and BCM<sup>115</sup>. Finally, an investigation performed on 42 children between the ages of 1.3-17.1 years, undergoing either an autologous or allogeneic BMT illustrated that muscle protein reserves were significantly reduced (11%) during the first month post-transplant, and it could take approximately six months for patients to reach pre-BMT levels<sup>385</sup>. While weight was gained during periods of parenteral nutrition, there was a simultaneous loss of skeletal muscle protein reserve.

In summary, energy deficits resulting in a loss of both FM and FFM occur when EE exceeds EI. Body composition of the patient, the relative size of the energy deficit and the effect of the disease will influence the partitioning between FFM and FM during weight loss<sup>123</sup>.

Although a reduction in body weight has been given much of the attention, cancer, treatment and/or psychosocial problems have the potential to increase body weight. Between 50-96% of early-stage breast cancer patients experience a significant weight gain of 2.5-6.2kg, with up to 10kg not uncommon<sup>96</sup>. Treatment-induced premature menopause, hormone treatment, changes in endocrine functioning, reduction in physical activity, elevations in energy intake and emotional reactions to cancer, are all plausible reasons for weight gain<sup>295</sup>. At present there is debate regarding the influence of body weight on prognosis<sup>377</sup>, although a consensus exists that an increase in body weight adversely affects women's self-esteem, feelings of inadequacy, insecurity, loneliness and social rejection. Additionally, the tendency toward weight gain consisted of both an increase in fat tissue and a loss in lean body tissue, thus contributing to a reduced functional capacity. Others have also reported a reduction in lean body mass (mean loss of 0.8kg) with a corresponding increase in percentage body fat (1.3%), in premenopausal and perimenopausal patients being treated with chemotherapy and radiotherapy for breast cancer<sup>198</sup>.

An investigation studying the effects of medroxyprogesterone on food intake and body composition in patients with advanced, nonhormone-sensitive cancer, found that the drug induced a positive influence on appetite and led to a significant increase in energy, protein, fat and carbohydrate consumption. This increase in food intake led to the reversal of ongoing fat loss, however it failed to improve the functionally important body component, lean tissue<sup>362</sup>. These data have been supported by other studies which found that sedentary patients on total parental nutrition may synthesise fat rather than lean tissue in contrast to those who exercise<sup>108</sup>. A further investigation performed on oral cancer patients demonstrated similar findings for weight gain<sup>26</sup>. Following treatment, patients experienced a mean weight loss of 10.8%, and more than three years post-treatment, 10 out of 25 patients had not returned to pre-treatment 'usual' weights. However, according to body mass index, 24 patients were either at or above the 'normal' level. Importantly, a change in weight distribution was found, with a greater proportion of body fat and lower proportion of FFM evident when compared with age- and sex-matched controls. The results suggested that regained weight is laid down predominantly as fat rather than lean tissue.

Although an important cause of weight loss is undoubtedly low caloric intake, the aetiology of wasting is more complex and multifactorial<sup>135</sup>. It is becoming evident that although adequate energy intake has the potential to slow, stop or even reverse body weight loss, an adequate food intake fails to correct or prevent loss of muscle mass that is associated with cancer and its treatment<sup>331</sup>.

#### **4.1.3 Impact of exercise on body weight and body composition**

The muscle atrophy and decrements in muscular strength caused by unloading is widely recognised<sup>297</sup>. Evidence provided above shows that nitrogen wasting caused by malnutrition, side effects of the disease and/or immobilisation, cannot be easily reversed by food alone. One area of potential optimism is the use of exercise in improving body composition status.

The effects of exercise on body composition in the 'healthy population' have been well documented<sup>300</sup>. While aerobic exercise is known for its role in reducing body

fat and maintaining lean tissue, resistance training is generally considered to be associated with improving lean tissue status.

Moderate exercise training has the capacity to increase the efficacy of dietary protein utilisation<sup>57</sup>. Nitrogen balance is maintained with normal protein intake. However, when protein intake is marginal, the rate of nitrogen retention is elevated when exercise of an intensity of 40-50% VO<sub>2</sub> max is added. An exercise intensity higher than this, however, can lead to a negative nitrogen balance, illustrating the importance of maintaining a moderate exercise intensity for cancer patients.

Animal research reported by Hicks (1990)<sup>161</sup> found that protein synthesis may be enhanced through exercise, even in the presence of malignancy. Protein turnover can be significantly altered by the presence of tumour in rats, to a greater extent than that caused by food restriction. Endurance exercise for seven weeks was shown to retard both muscle mass depletion and tumour growth.

An investigation with HIV-patients was conducted to study the effects of an anabolic steroid treatment in conjunction with a resistive exercise program on body composition. All study participants received the drug and were randomised to either a progressive resistance exercise group or control group. Unfortunately the study did not include an exercise-only group. Nevertheless, the results showed that by the end of the first month, six control subjects gained 1.9% of entry weight, one subject lost weight, and two lost BCM. In contrast, seven subjects in the exercise group demonstrated a 3.2% increase of entry weight and no subject within the exercise group showed any declines<sup>323</sup>. In another study with HIV-1 patients (Spence et al, 1990 in Lox et al, 1996<sup>222</sup>), following a six week progressive resistance training program, muscular strength for the regions of the legs, chest, shoulder and arms, significantly improved pre- to post-program for those in the exercise group. The exercising patients at post-program also experienced significantly higher levels of muscular strength when compared with the control group. Of particular interest, for those in the control group, muscular strength was either unchanged or declined following the six week period. In addition, body weight and girth measurements increased for the experimental group, while the control group showed significant decreases for these variables.

In yet another HIV-1 and AIDS investigation (Rigsby et al, 1992 in Lox et al, 1996<sup>222</sup>), it was shown that improved cardiovascular and anthropometrical status can occur with the integration of both aerobic and strength exercises. The experimental participants demonstrated a 30% improvement in muscular strength following a 12-week program. In contrast, no significant changes were found for the control participants.

Lastly, an investigation studying the effects of an aerobic-only, a strength training program-only and a stretching control group on body composition and fitness was undertaken on HIV-1 males<sup>222</sup> and provided supporting evidence<sup>222</sup> for the above studies. The aerobic-only group demonstrated the highest fitness changes, and the strength training group demonstrated the highest muscular strength gains. Both groups demonstrated losses in fat mass and gains in FFM, with the aerobic group illustrating the higher fat mass losses and the strength group higher FFM gains. While these results demonstrate the principle of training specificity, the results observed also illustrate that a certain level of 'crossover' can occur. That is, those in the exercise group also showed partial improvements in leg strength, and the weight training group showed partial improvements in cardiovascular training. As was expected, the changes in body composition mirrored the changes observed in muscular strength. Importantly, these results also demonstrated the notion that inactivity is associated with physiological declines, as was evidenced by the decline in fitness and muscular strength in the control group. The collaborative results of the above investigations provide important evidence for the potential for exercise to be used to correct or combat the wasting process associated with disease and treatment.

Furthermore, exercise can also have the alternative effect in weight maintenance, whereby weight gain and muscle wasting can be reduced through exercise<sup>226</sup>. Weight stabilisation, and improved weight and skinfold thickness have been shown in exercising breast cancer patients following a ten week cycle ergometry protocol<sup>226</sup>, and an eight week aerobic protocol<sup>429</sup>, respectively. A later investigation demonstrated that exercising breast cancer patients (patients exercised 20-30 minutes, three times per week for 10-12 weeks) experienced a reduction in

percentage body fat and an increase in lean body mass, even though both control and exercising patients attained a slight increase in total body mass<sup>428</sup>.

#### 4.1.4 Use of body composition assessment methods

The above research clearly demonstrates the importance of assessing body composition, rather than just body weight changes in the clinical setting. However, for body composition to become a commonly measured variable throughout the cancer continuum, practical assessment techniques need to be identified. Unfortunately, numerous difficulties exist in accurately monitoring body composition changes in cancer patients<sup>177</sup>. An increase in hydration and changes in potassium concentration observed in these patients have the capacity to invalidate many of the classical methods used to determine body composition<sup>177</sup>. It has been suggested (Cohn et al, 1981 in Reilly and Workman, 1994<sup>316</sup>) that the wasting associated with many cancer states leads to a higher than expected water content of the FFM, due to the loss of BCM with a relative expansion of the extracellular fluid. In addition, measurement of total body potassium to determine body composition is problematic in cancer patients experiencing muscle wasting, since muscle is relatively rich in potassium. Of specific relevance to this investigation are PBST patients, and it has been reported that bone marrow transplant patients frequently experience fluid weight shifts post-transplant<sup>68</sup>.

Two methods, bioelectrical impedance analysis (BIA) and skinfolds, are available for use within the clinical setting to assess body composition, and are based on a two compartment model comprising FM and FFM<sup>364</sup>. It was identified in two investigations with both normal and underweight cancer patients that the single-frequency BIA parameter  $ht^2/R$ , maintains a high correlation with total body water as assessed via deuterium dilution<sup>363, 364</sup>. However, an important problem identified was that the BIA systematically overestimated total body water in underweight patients when a prediction formula, developed from normal-weight subjects, was applied<sup>364</sup>.

The second technique, the use of skinfolds is relatively inexpensive and is considered to be accessible and precise, when implemented using a trained observer<sup>316</sup>. Apart

from tester skill, reliability of this technique is also dependent on the standardisation of the skinfold calipers and the use of appropriate age- and sex-specific equations<sup>301</sup>. However, one source of potential error that specifically relates to its use within the cancer population is that the method depends on the relationship between subcutaneous adiposity and total body fat being similar to that in the original healthy population upon which the predictive equations are based<sup>316</sup>. It is plausible that in a number of oncology populations fat distribution may be altered, as may the relationship between subcutaneous fat and total body fat. The practical significance of this error source is as yet unknown and future research in this area is required. To date, no work could be identified throughout the literature that compared the calculation of percentage body fat using various techniques in the oncology setting.

## 4.2 Methodology

Chapter 3 provided a detailed outline of the methodological procedures that relate to subject recruitment, the testing phases and the intervention program implemented. In summary, 12 patients, with 6 patients in each group were recruited. Of these, only 7 patients were recruited at PI, while the remaining subjects entered the investigation at PII. Outlined below are the methodological procedures which relate specifically to the aims of this section of the investigation and involve anthropometric, body composition, energy expenditure and food frequency intake measures.

### 4.2.1 Height, weight and body mass index

Height and weight were measured to the nearest 0.1cm and 0.01kg, respectively. The variables were assessed with the subjects barefoot and were measured using a wall mounted Harpenden stadiometer™ (Holtain Ltd, Crymych, Dyfed) and a calibrated digital electric scale, Wedderburn Scales™ (Tanita BWB-600). Body mass index (BMI) was calculated from the formula,  $\text{weight(kg)/height}^2(\text{m}^2)$ .

### 4.2.2 Body composition

A number of factors limit the accuracy of measuring body composition in patients with cancer<sup>177</sup>. Therefore, 2 techniques, the skinfold method and singly labeled water method, were employed to assess %BF, FM and FFM in order to improve the reliability of the data.

#### 4.2.2.1 Singly labelled water technique

The calculation of body composition is often derived from the measurement of total body water (TBW). One method of assessing TBW is through the use of the deuterium dilution technique.

The calculation of the total body water volume is based on the following simplified relationship<sup>27</sup>:

$$C_1 * V_1 = C_2 * V_2$$

or

$$V_2 = C_1 * \frac{V_1}{C_2}$$

where:  
 $C_1$  = initial concentration of ingested or injected tracer  
 $V_1$  = initial volume of ingested or injected tracer  
 $C_2$  = final concentration of tracer in blood or urine  
 $V_2$  = volume of total body water

In order to minimise error associated with dosing, a 10% stock dose solution was made and then autoclaved (EA-652 Bench Type Autoclave, Medical & Surgical Requisites Pty Ltd, Brisbane, Australia). A 5ml sample was then taken from the autoclaved dose for calibration and frozen until required. Each subject received a dose of 0.5g/kg body weight following collection of a pre-dose urine sample. The pre-dose urine sample was used to assess background levels of isotopic enrichment, and it was assumed that these levels remained constant throughout the study period of four to six hours. Following ingestion of the dose, the bottle was then reweighed to the nearest 0.001g, to ensure that the exact dose ingested could be calculated. Between 4-6 hours post-dose ingestion, the subject was required to provide a second urine sample and to record the exact time the sample was taken. The two urine samples were then kept frozen until required for assessment.

The isotope enrichment of the pre-dose urine sample, the post-dose urine sample, local tap water and a sample of the dose given, were measured in triplicate samples by using a gas isotope ratio mass spectrometer (Hydra PDZ Europa Scientific, Crew, UK). When using deuterium dilution, two approaches can be implemented to calculate TBW and include either the plateau or back-extrapolation method. Both methods have previously been examined and have been found to yield similar results<sup>90</sup>. The plateau method, which involves calculating the dilution space by subtracting the pre-dose urine sample enrichment from the four to six hour post-dose enrichment, was applied in this investigation. The enrichment then represents the

concentration of the administered tracer in the body, and by taking into account the weight of the dose given, can be used to determine the volume of the dilution space.

The equation used to calculate the dilution space ( $N$ ) is as follows:

$$N = \frac{TA*(Ea-Et)}{a*(Es-Ep)}$$

Where:

- $A$  = isotope in grams for mass spectrometer analysis,
- $a$  = the portion of the dose in grams retained for mass spectrometer analysis,
- $T$  = the amount of tap water in which the portion of  $a$  is diluted before analysis,
- $Ea$  = isotopic enrichment in delta units of the portion of the dose
- $Et$  = isotopic enrichment in delta units of the tap water used
- $Ep$  = isotopic enrichment in delta units of the pre-dose urine sample
- $Es$  = isotopic enrichment in delta units of the post-dose urine sample

Delta units express isotopic enrichment relative to a standard, standard mean ocean water (SMOW). The dilution space assessed exceeds TBW due to the exchange of the tracer with non-aqueous hydrogen atoms within the body. The difference in humans is believed to be 3-4%<sup>90</sup> and hence, the <sup>2</sup>H dilution space can be converted to TBW by dividing TBW by 1.04.

When using this method, FFM is calculated by dividing the measured TBW by 0.73, the assumed hydration coefficient of the FFM in normal-weight healthy individuals. FM is subsequently calculated by subtracting FFM from body weight. While limited data is available on the hydration coefficient of the FFM in normal-weight or underweight cancer patients, Simons and colleagues (1998)<sup>362</sup> reported unpublished laboratory work demonstrating that, through the use of deuterium dilution and DEXA-scanning, the hydration coefficient of lung carcinoma patients (mean BMI, 20.8) was 0.73±0.03 (range = 0.68-0.79). Therefore, to extrapolate to body composition, the following formula was applied:

$$FFM = TBW \text{ (litres)}/0.73$$

Thus,

$$FM = BW - FFM.$$

#### 4.2.2.2 Skinfold technique

Jackson and Pollock (1985)<sup>174</sup> have simplified the calculation of %BF by providing tabulated percentage body fatness values for different skinfold thicknesses across various age groups<sup>305</sup>. All that is required for %BF and thus FM and FFM to be determined is the sum of skinfolds (SOS). The same qualified tester (accredited at Level 1 Anthropometry) assessed six standard skinfolds (triceps, biceps, subscapular, abdominal, supraspinale and medial calf) at each of the three testing periods, in order to ensure that the procedure was standardised and implemented with reliability and objectivity. The specific details relating to the assessment of each skinfold site has been provided in Appendix V. Each skinfold site was assessed twice and the technical error of measurement (TEM) followed by the relative TEM (%TEM) was calculated and recorded at less than 5%. The procedure used to calculate the absolute and relative TEM has been described by Norton & Olds (1996)<sup>271</sup>. The mean of the two skinfold scores for each site was used in the SOS calculation, which was derived from the addition of all six skinfolds sites. Tabulated data allowed the calculation of %BF from the SOS and the patient's age. Body weight and %BF were then used to calculate FM and FFM.

#### 4.2.3 Energy expenditure – doubly labelled water technique

The premise of the doubly labeled water (DLW) method is that O atoms in expired CO have isotopically equilibrated with the O atoms in body water. Thus, following a loading dose of <sup>2</sup>H and <sup>18</sup>O water, the <sup>2</sup>H is eliminated from the body as water, mainly as urine, while the <sup>18</sup>O is eliminated as water and CO<sub>2</sub>, in an exponential fashion. The rapid equilibration of oxygen between water and carbon dioxide leads to the elimination via carbon dioxide. The difference between the elimination rates from the body water pool, after adjusting for isotopic fractionation, is therefore proportional to CO<sub>2</sub> production and hence energy expenditure can be calculated<sup>74, 273, 341</sup>. A primary underlying assumption of the technique is that the hydrogen and oxygen of water are only lost from the body water pool as water and carbon dioxide<sup>313</sup>. Error will be introduced in the calculation of rCO<sub>2</sub>, if any other exchange or transformation in the body occurs. An example would be if deuterium is incorporated into protein or fat during reductive biosynthesis which would cause an

overestimate of water flux and an underestimate of the difference between  $^2\text{H}$  and  $^{18}\text{O}$  fluxes, and thus an underestimate of  $r\text{CO}_2$ . A review of the literature performed by Haggarty (1988) and reported by Ravussin (1991)<sup>313</sup> found that the maximum error on rates of  $\text{CO}_2$  due to fat synthesis was 5%.

The doubly-labelled water technique is considered a valid tool for assessing energy expenditure in various populations including infants, young adults, healthy adults, and patients with gastrointestinal disorders, and subjects under metabolic ward conditions<sup>340</sup>. The accuracy (1-2% with a relative standard deviation of 3-9%) and precision (approximately 4%) of the technique have also previously been shown<sup>90</sup>.

A mixed dose containing 0.125g/kg 100%  $\text{H}_2^{18}\text{O}$  and 0.05g/kg 100%  $^2\text{H}_2\text{O}$  was given orally to each subject following the collection of a pre-dose urine sample. In each case the weight of the dose ingested in grams was determined to three decimal places through the use of Mettler Todedo PB3002 scales<sup>TM</sup> (Switzerland). Urine specimens were then collected 4-6 hours post-dose and thereafter at daily intervals for 14 days. The time of each urine sample was accurately recorded on data sheets provided to the patients, and the patients noted whether they had experienced any vomiting or diarrhoea on any day. Urine samples were stored in the freezer (collection tubes and container bags were provided) and the samples were collected at the end of the 14 days by the researcher. While 16 samples were collected, triplicate samples were only assessed for the pre- and post dose-samples and day 1, 2, 3, 11, 12, 13 and 14 samples.

Isotopic enrichment of the urine samples was measured relative to local standards by isotope ratio mass spectrometry (Hydra PDZ Europa Scientific, Crew, UK). The sensitivity of isotope ratio mass spectrometer measurements is achieved by comparing the isotopic abundance of the sample to that of a reference gas under identical measurement conditions. Results are expressed in delta units or as ‰ (per mil) enrichment relative to SMOW. Thus,

$$\delta \text{ enrichment} = [(R_s/R_r) - 1] * 10^3$$

Where:  $R_s$  = the ratio of isotopes in the sample, ie  $^2\text{H}/^1\text{H}$ ,  
 $R_r$  = is the ratio of isotope in the reference (SMOW)  
( $^2\text{H} = 0.00015595$ ,  $^{18}\text{O} = 0.002005$ )

Linear regression equations were obtained from the log transforms of measured enrichments of  $^2\text{H}$  and  $^{18}\text{O}$  across time minus the predose. The regression coefficients are therefore the disappearance rates,  $k_d$  and  $k_o$  of  $^2\text{H}$  and  $^{18}\text{O}$ , respectively. The dilution space of each isotope ( $N_o$ ,  $N_d$ ) at the beginning of the study period is calculated as:

$$N = \frac{TA}{a} * \frac{E_a - E_t}{E_s}$$

Where:  $N_o$  = the  $^{18}\text{O}$  dilution space, and  
 $N_d$  = the deuterium dilution space,  
 $A$  = the dose of isotope given,  
 $a$  = a portion of the dose diluted for mass-spectrometric analysis, in a mass,  
 $T$  = of tap water.  
 $N$ ,  $T$  and  $A$  are in grams.  
 $E_a$  = enrichment of the portion,  
 $E_t$  = enrichment of tap water,  
 $E_s$  = the antilog of the intercept of the regression line.

Output rates of carbon dioxide,  $r\text{CO}_2$  (mole/day) corrected for fractionation effects were calculated using a constant value for the proportion of water fractionated ( $x$ ) and values for the fractionation of  $^2\text{H}$  and  $^{18}\text{O}$  ( $f_1$  and  $f_2$ ) in water vapour and  $^{18}\text{O}$  ( $f_3$ ) in  $\text{CO}_2$ . The value of  $x$  used in the present study was 0.25 and the values for  $f_1$ ,  $f_2$ , and  $f_3$  were 0.941, 0.993 and 1.040, respectively<sup>90</sup>.

Carbon dioxide production rate was calculated as,

$$r\text{CO}_2 = \frac{N_o k_o - N_d k_d (1 + (f_2 - f_1)x)}{2f_3}$$

Assuming a respiratory quotient of 0.85, total energy expenditure was calculated using Weir's formula<sup>418</sup>.

#### 4.2.4 Dietary assessment

A food frequency questionnaire (Table 4.1) was designed and administered by the investigator, to evaluate the number of servings of vegetables, fruits, breads and cereals, meat products, dairy products, snacks and beverages consumed per day, over the past week. Detailed dietary analysis was considered beyond the scope and intent of this thesis and thus the dietary assessment was initiated merely to obtain a broad

indication of food intake. Therefore, in the design of the questionnaire, no attempt was made to classify the size of the servings or the number of calories consumed per day, nor was the questionnaire validated. The questionnaire required the subject to circle a response relating to specific food groups, that best represents their nutritional habits at the time of completing the questionnaire.

**Table 4.1** Dietary intake questionnaire

Please circle, which of the following best represents your nutritional habits:

	Frequency				
	>2 servings per day	1-2 servings per day	At least 2 servings, 4-6 x week	At least 2 servings, <4 x week	Rarely
Vegetables – 1 serving = a portion of any vegetable	>2 servings per day	1-2 servings per day	At least 2 servings, 4-6 x week	At least 2 servings, <4 x week	Rarely
Fruit – 1 serving = a piece of any fruit	>2 servings per day	1-2 servings per day	At least 2 servings, 4-6 x week	At least 2 servings, <4 x week	Rarely
Breads and cereals – 1 serving = 2 slices of bread or a bowl of cereal	>2 servings per day	1-2 servings per day	At least 2 servings, 4-6 x week	At least 2 servings, <4 x week	Rarely
Meat products – 1 serving = a portion of red or white meat, or fish	>2 servings per day	1-2 servings per day	At least 2 servings, 4-6 x week	At least 2 servings, <4 x week	Rarely
Dairy products – 1 serving = a glass of milk, a tub of yoghurt, 2 slices of cheese etc	>2 servings per day	1-2 servings per day	At least 2 servings, 4-6 x week	At least 2 servings, <4 x week	Rarely
Snack foods including cakes, sweets, lollies, chocolates, chips, etc	>2 per day	1-2 per day	At least 1, 4-6 x week	At least 1, <4 x week	Rarely
Number of beverages	>6 per day	4-6 per day	2-3 per day	one per day	<1 per day

#### 4.2.5 Statistical analysis

Data for total energy expenditure, body composition and food intake frequency were collected at each of the three testing phases, and TEE and body composition data were analysed according to the statistical procedures outlined in Chapter 3. Food

frequency data was assessed by reporting the number of patients within the study group at PI and PII, and the control and exercise groups at PI, PII and PIII, who consumed a specific number of servings per food group. In this manner, changes in food frequency consumption across the testing phases could be observed.

Finally, a Pearson's product moment was used to determine the relationship between %BF calculated via the use of the skinfold and SLW technique, while the Bland Altman technique<sup>40</sup> was employed to calculate the agreement between the two methods. This technique required several calculations:

- calculating the difference between %BF recorded for the two techniques (skinfold and SLW) ( $a$ );
- calculating the mean of %BF recorded for the two techniques ( $b$ );
- plotting  $a$  (y axis) against  $b$  (x axis);
- calculating the mean of the differences ( $x$ ) and SD of the differences ( $s$ );
- and, provided the differences lie within  $x \pm 2s$ , the limits of agreement can be calculated:

$$\begin{aligned}x - 2s &= y_1 \\x + 2s &= y_2\end{aligned}$$

### 4.3 Results

The changes in body composition and energy expenditure for patients undergoing a PBST are presented in Table 4.2. The treatment is associated with significant decreases in weight ( $p<0.01$ ) and BMI ( $p<0.01$ ) (Figure 4.2 and 4.3). Although there was no significant change in %BF by use of the skinfold technique, significant decreases in FM ( $p<0.05$ ) and FFM ( $p<0.01$ ) were shown. When body composition was assessed via the deuterium dilution technique, FFM decreased ( $p<0.05$ ). No significant decrease was observed between the pre- and post-transplant testing phases for energy expenditure.

**Table 4.2** Body composition and energy expenditure measures at PI and PII for the study group (mean $\pm$ SE)

Study Group	PI n = 7		PII n = 12		p value
Variable	Mean	SE	Mean	SE	
Wt (kg)	87.6	1.4	79.5	0.9	0.000**
BMI (wt/ht <sup>2</sup> )	29.9	0.5	27.2	0.3	0.000**
Skinfold technique:					
BF (%)	27.9	0.8	26.2	0.5	0.085
FM (kg)	22.4	0.8	20.1	0.5	0.030*
FFM (kg)	55.7	0.7	52.5	0.4	0.003**
Singly-labelled water technique:					
BF (%)	34.3	1.5	33.6	1.1	0.736
FM (kg)	32.1	1.9	28.5	1.4	0.142
FFM (kg)	54.8	1.3	51.1	0.9	0.036*
TEE (kcal/day)/FFM(kg) <sup>0.5</sup>	284 (n=4)	84.6	260 (n=4)	84.6	0.104

\*  $p<0.05$ , \*\*  $p<0.01$

The high levels of body fat found in certain patients prevented the repeatable measurement of %BF, FM and FFM, via the use of the skinfold technique for these particular patients. Consequently, there were greater missing data derived from the skinfold technique, when compared with the SLW technique. That is, repeatable measurements for body composition were collected from 12 patients using the

deuterium dilution method, compared with only 8 patients when using the skinfold technique. Further data analysis and reporting of results therefore only relates to the data collected via the SLW technique.

Table 4.3 shows body composition changes across the testing phases for the control group. The patients in the control group showed significant changes in weight ( $p < 0.05$ ) and BMI ( $p < 0.05$ ) between pre- and post-treatment. Three-months post-transplant, weight and BMI remained significantly lower ( $p < 0.05$ ) than pre-transplant measures. Mean changes were observed in %BF, FM or FFM across the testing phases, however these were not statistically significant.

**Table 4.3** Body composition measures across the testing phases for the control group (mean $\pm$ SE)

Variable	Phase	Mean	SE	Comparisons	p value
Wt (kg)	I	78.6	2.2	PI - PII	0.017*
	II	71.8	1.4	PI - PIII	0.041*
	III	72.8	1.6	PII - PIII	0.573
BMI (wt/ht <sup>2</sup> )	I	27.7	0.8	PI - PII	0.013*
	II	25.3	0.5	PI - PIII	0.032*
	III	25.7	0.6	PII - PIII	0.540
%BF	I	33.7	2.5	PI - PII	0.687
	II	32.4	1.6	PI - PIII	0.628
	III	32.1	1.8	PII - PIII	0.876
FM (kg)	I	27.2	3.1	PI - PII	0.318
	II	24.8	1.9	PI - PIII	0.416
	III	25.1	2.2	PII - PIII	0.867
FFM (kg)	I	51.5	2.1	PI - PII	0.145
	II	47.0	1.3	PI - PIII	0.213
	III	47.0	1.8	PII - PIII	0.996

n = PI - 3; PII - 6; PIII - 5

\*  $p < 0.05$

Table 4.4 demonstrates changes in body composition and EE observed across the testing phases for the exercising group. Weight, BMI and FM were significantly lower at PIII ( $p < 0.05$ ) when compared with pre-transplant data. Following the exercise intervention program, FFM significantly increased ( $p < 0.01$ ) while %BF significantly decreased ( $p < 0.05$ ). Additionally, by three months post-transplant, exercising patients were expending a significantly greater ( $p < 0.01$ ) amount of energy when compared with pre- and immediately post-treatment.

**Table 4.4** Body composition and energy expenditure measures across the testing phases for the exercise group (mean $\pm$ SE)

Variable	Phase	Mean	SE	Comparisons	p value
Wt (kg)	I	96.7	1.8	PI - PII	0.007**
	II	87.4	1.4	PI - PIII	0.028*
	III	89.7	1.4	PII - PIII	0.315
BMI (wt/ht <sup>2</sup> )	I	32.3	0.6	PI - PII	0.010*
	II	29.2	0.5	PI - PIII	0.033*
	III	29.9	0.5	PII - PIII	0.369
%BF	I	34.9	1.8	PI - PII	0.980
	II	34.8	1.6	PI - PIII	0.051
	III	29.5	1.6	PII - PIII	0.041*
FM (kg)	I	37.0	2.2	PI - PII	0.201
	II	32.2	1.9	PI - PIII	0.032*
	III	28.2	1.9	PII - PIII	0.245
FFM (kg)	I	58.4	1.5	PI - PII	0.140
	II	55.1	1.3	PI - PIII	0.152
	III	61.6	1.3	PII - PIII	0.008**
TEE (kcal/day)/FFM(kg) <sup>0.5</sup>	I	284	11	PI - PII	0.185
	II	260	11	PI - PIII	0.004**
	III	356	11	PII - PIII	0.001**

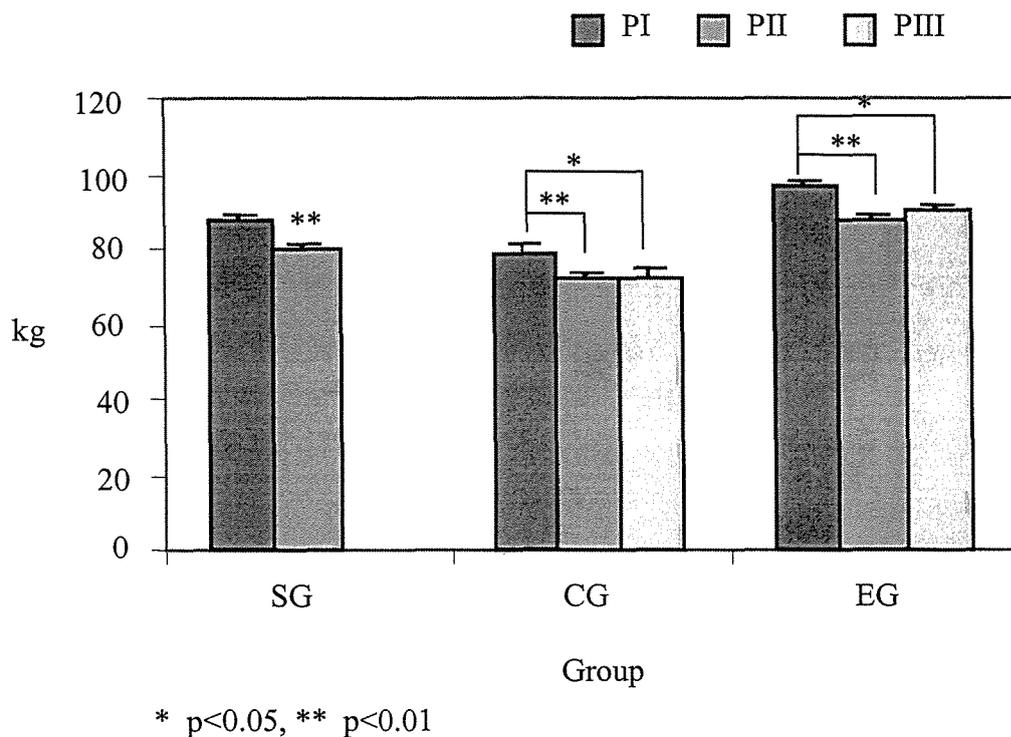
n = PI - 4; PII - 6; PIII - 6

\*  $p < 0.05$ , \*\*  $p < 0.01$

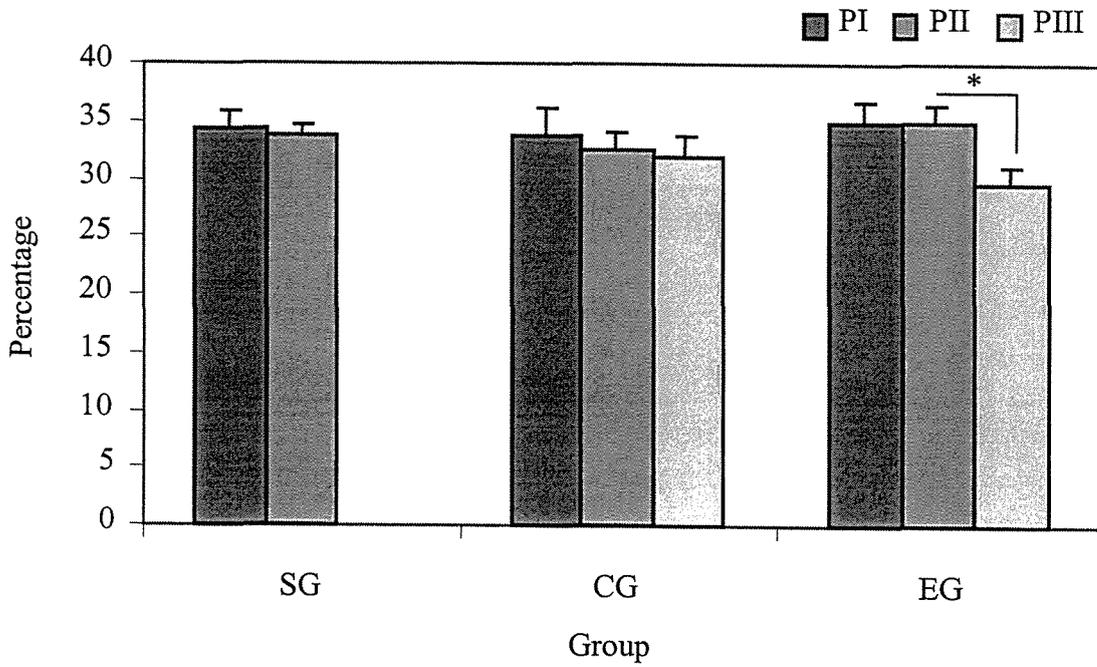
Changes in weight and body composition across the testing phases for both groups are presented in Figure 4.2a, b, c and d. Individual changes of FFM for the subjects in the control and exercise groups are presented in Figure 4.2e. A mean reduction in weight (Figure 4.2a), %BF (Figure 4.2b), FM (Figure 4.2c) and FFM (Figure 4.2d) are observed following the transplant. However, only the changes detected in weight and FFM during the pre- and post-transplant period were significant ( $p < 0.01$  and  $p < 0.05$ , respectively). Weight remained ( $p < 0.05$ ) lower for both the control and exercising patients at three months post-treatment. Mean decreases in %BF ( $p < 0.05$ ) and FM, and a significant increase ( $p < 0.01$ ) in FFM, were also detected following participation in the exercise intervention program. All subjects in the exercise group displayed a similar trend for change in FFM across the testing phases (Figure 4.2e). As is also shown in Figure 4.2e, 4 out of 5 subjects in the control group displayed either no change or a mean increase in FFM during the 3-months post-transplant, while 1 patient demonstrated a mean loss of FFM.

**Figure 4.2** Changes in weight and body composition for the study group (PI & PII), and the control and exercise groups (PI, PII & PIII) (mean $\pm$ SE)

(a) Changes in weight

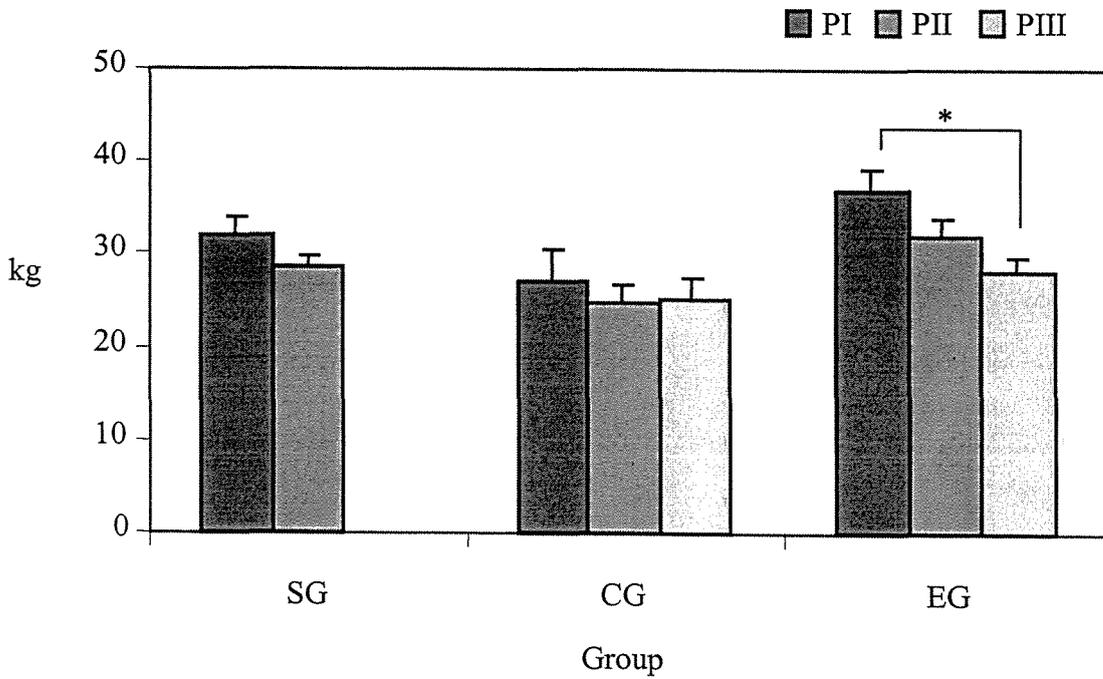


(b) Changes in percentage body fat



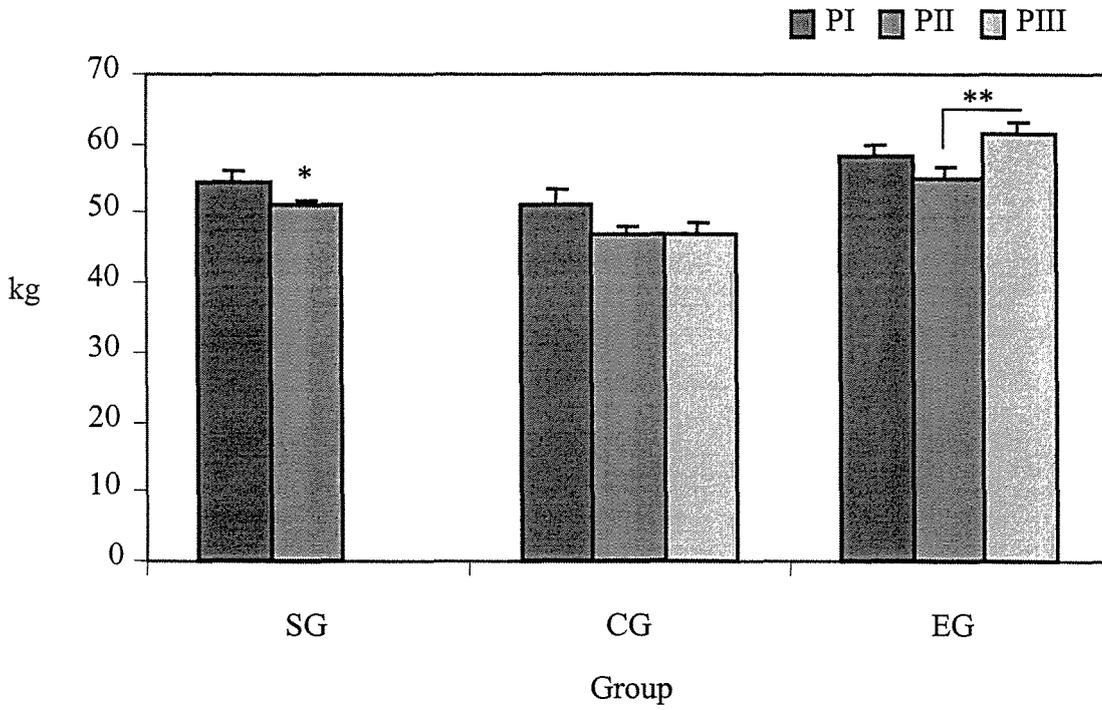
\*  $p < 0.05$

(c) Changes in fat mass



\*  $p < 0.05$

(d) Changes in fat free mass



\*  $p < 0.05$ , \*\*  $p < 0.01$

(e) Individual changes in FFM across the testing phases (PI, PII & PIII) for subjects in the control and exercise group

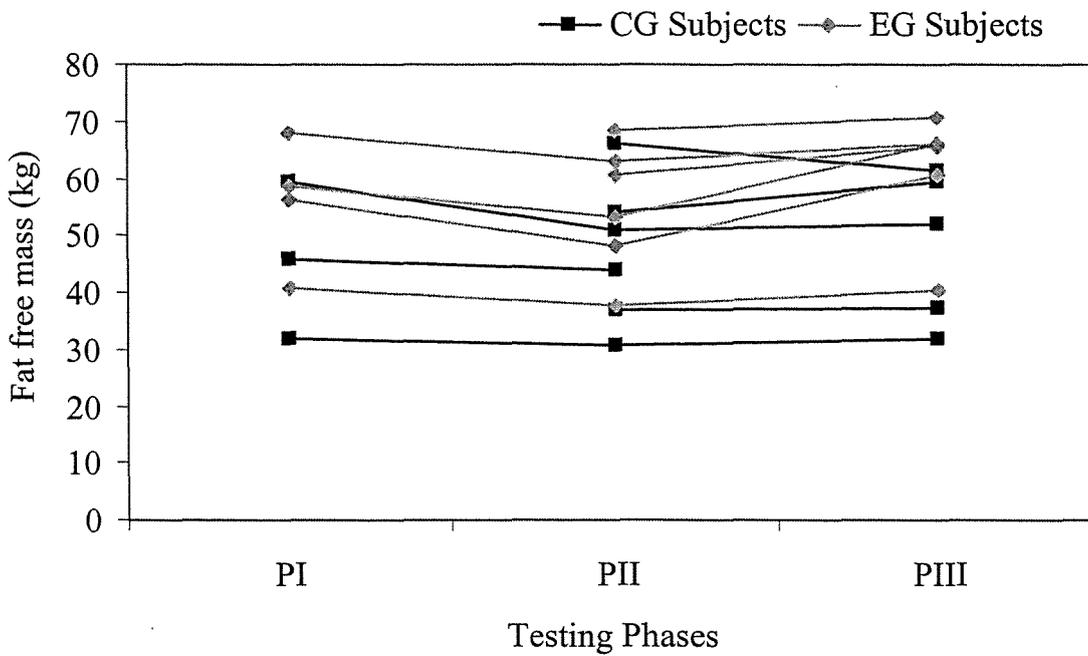
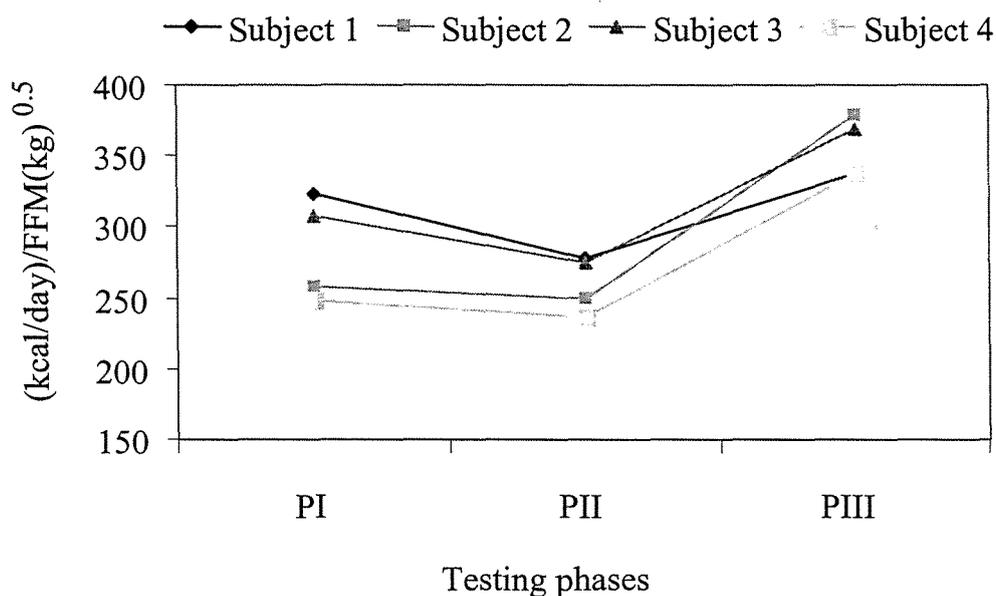


Figure 4.3 displays the TEE results recorded from four subjects in the EG. A Pearson correlation performed on FFM and TEE data ( $R=0.60$ ,  $p<0.05$ ) indicated that the level of FFM measured influenced TEE. Since the FFM of the subjects altered across the three testing phases, it was deemed crucial to appropriately adjust TEE with regard to these FFM fluctuations. A common method of adjusting for FFM changes is by dividing TEE by FFM. However, a second negative correlation ( $R=-0.56$ ,  $p<0.05$ ) applied to TEE/FFM and FFM indicated that a ratio of TEE and FFM may not adequately account for FFM changes. In order to find an appropriate method of adjusting for FFM changes, TEE and FFM values were log-transformed and analysed by linear regression. The coefficient calculated in this case, is the power to which FFM must be raised to completely adjust TEE for FFM. Since the linear regression coefficient was within 2 standard errors of either 0.5 or 1, TEE can be adjusted for FFM by expressing TEE per FFM  $(\text{kg})^{0.5}$  or alternatively,  $\text{TEE}/\sqrt{\text{FFM}(\text{kg})}^{89}$ .

Across the sampling periods there were no incidences of vomiting or diarrhoea, which could have potentially influenced the results. No change was observed in TEE as a consequence of undertaking a PBST. However, TEE significantly increased ( $p<0.01$ ) by three months post-PBST. Results for TEE at PIII was also significantly higher ( $p<0.01$ ) than that measured at PI.

**Figure 4.3** Changes in TEE for four subjects in the exercise group across the testing phases (TEE at each phase for each subject)



A Pearson correlation performed on %BF data (Table 4.5) recorded by the use of skinfolds and SLW demonstrated that the two techniques were significantly related ( $R=0.885$ ;  $p=0.000$ ).

**Table 4.5** Pearson correlation of percentage body fat techniques

n = 24	Mean	SD	Pearson correlation	p value	t value	p value
%BF (Skinfolds)	25.8	9.1	0.885	0.000	-4.513	0.000**
%BF (SLW)	29.9	9.5				

\*\*  $p < 0.01$

However, the skinfold technique consistently recorded significantly lower values for %BF, when compared with the values recorded using SLW. Thus, a high correlation does not necessarily mean agreement between the two methods. In order to calculate the agreement between the two methods the Bland Altman technique was employed<sup>40</sup>. Figure 4.4 illustrates that the limits of agreement lie between 21.56% and -30.26%.

**Figure 4.4** Bland Altman Plot displaying the limits of agreement between the skinfold and SLW technique

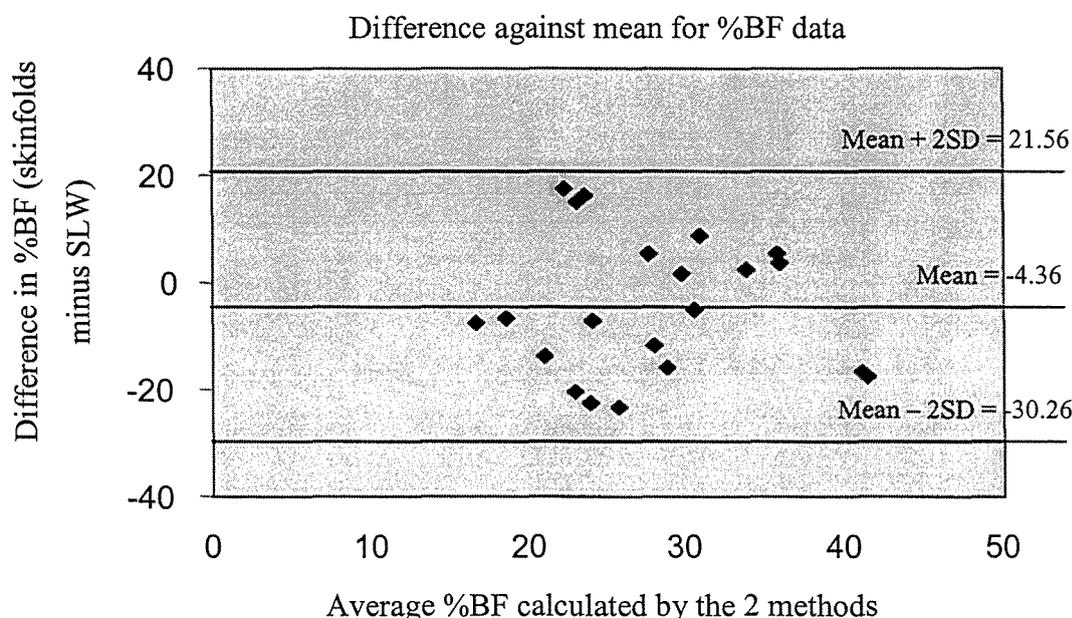


Table 4.6 displays the change in the frequency of food group consumption per day following a PBST and a three-month intervention period post-transplant. Data collected from the entire study group (SG) is presented for PI and PII, while PIII data has been presented for both the control and exercising group. No statistical procedure was employed to analyse the changes in the frequency of food group consumption per day, across the phases.

Undertaking a PBST was associated with a reduction in the number of patients who reported eating more than one serving of each food type assessed (vegetables: PI=5 patients, 72%; PII=6 patients, 50%; fruit: PI=4 patients, 57%; PII=5 patients, 42%; bread: PI=7 patients, 100%; PII=8 patients, 67%; dairy products: PI=6 patients, 89%; PII=5 patients, 42%; and meat: PI=5 patients, 72%; PII=3 patients, 25%). Fewer patients were also snacking and consuming fluids. By three-months post-transplant, patients in both the control and exercising group demonstrated an increase in the number of food servings ingested per day. In the CG, 80%, 40%, 80%, 60%, and 40% of patients ate greater than one serving of vegetable, fruit, bread, dairy and meat products, respectively, per day. In the EG, 83%, 66%, 88%, 83% and 33% of patients ate more than one serving of vegetable, fruit, bread, dairy and meat products per day.

**Table 4.6** The number of patients consuming a certain quantity of major food group servings per day over the past week

Group and Phases	n	Number of patients within the group who have consumed a certain number of servings per day over the past week				
		>2 servings/day	1-2 servings/day	min of 2 servings, 4-6 x wk	1-2 servings, 4-6 x wk	Rarely
<b>Vegetables</b>						
SG PI	7	5	-	2	-	-
SG PII	12	2	4	6	-	-
CG PIII	5	4	-	1	-	-
EG PIII	6	1	4	1	-	-
<b>Fruit</b>						
SG PI	7	3	1	1	1	1
SG PII	12	2	3	1	2	4
CG PIII	5	2	-	1	-	2
EG PIII	6	2	2	1	-	1
<b>Bread Products</b>						
SG PI	7	3	4	-	-	-
SG PII	12	3	5	2	1	1
CG PIII	5	4	-	5	-	-
EG PIII	6	3	2	1	-	-
<b>Dairy Products</b>						
SG PI	7	1	5	1	-	-
SG PII	12	1	4	5	1	1
CG PIII	5	-	3	1	-	1
EG PIII	6	1	4	1	-	-
<b>Meat</b>						
SG PI	7	-	5	2	-	-
SG PII	12	1	2	7	-	2
CG PIII	5	-	2	3	-	-
EG PIII	6	-	2	3	1	-
<b>Snacks</b>						
SG PI	7	1	2	2	1	1
SG PII	12	-	4	-	3	5
CG PIII	5	-	3	-	1	1
EG PIII	6	1	1	-	1	3
<b>Drinks</b>						
SG PI	7	3	4	-	-	-
SG PII	12	1	8	3	-	-
CG PIII	5	3	2	-	-	-
EG PIII	6	4	2	-	-	-

SG = study group; CG = control group; EG = exercise group

## 4.4 Discussion

The results of this investigation demonstrated that TEE and body composition altered following a PBST and participation in a three-month exercise intervention program. Adverse changes in body composition were associated with a PBST, as was evident by the losses observed in both BW and FFM at PII. Only those patients who participated in the exercise intervention were able to regain FFM by three months post-transplant. While participation in the exercise program increased TEE to levels higher than that experienced pre-transplant, body composition was not adversely influenced.

### 4.4.1 Body composition and total energy expenditure

Significant fluctuations in body weight experienced by the study group highlighted the presence of an energy imbalance between PI and PII. The TEE recorded from four patients during this same period decreased, however the reduction was not significant. Three months post-treatment, body weight remained significantly lower than pre-transplant levels. During this same period, TEE recorded by PIII had significantly increased and was statistically higher than pre-transplant levels.

Similar changes in TEE identified here were also found by the use of the labelled bicarbonate-urea technique in small cell lung cancer patients<sup>177</sup>. Following treatment, TEE decreased as a consequence of an elevation in REE in conjunction with a decrease in spontaneous activity, when compared to matched controls. Through the use of heart rate recordings, TEE and physical activity levels have also been assessed in long-term survivors of childhood malignancies<sup>410</sup>. Reductions in TEE, when compared with healthy siblings and as explained by reduced patterns of physical activity, were found. This continued decline in TEE adversely influenced body composition. Taken together, the results indicated that unless patients actively work towards readjusting TEE following cancer treatment, the energy imbalance has the potential to produce longer-term adverse consequences. In contrast to the reduction in TEE observed following treatment, an increase in TEE has also been reported following radiation and chemotherapy treatment for breast cancer<sup>201</sup>. However, these increases were considered 'slight and insignificant'.

While a relationship between REE and FFM has been previously shown, with the results indicating that the lower the FFM, the lower the REE<sup>195</sup>, studies of patients with unresectable pancreatic cancer have shown that body weight losses can also occur in the presence of increases in REE<sup>115</sup>. Therefore, although patients in this investigation showed a reduction in body weight and FFM following the PBST, it cannot be assumed that REE also declined. Decreases in REE are not consistent findings, with the literature reporting increased, decreased and normal states following cancer treatment. Factors including the type of tumour, the type of treatment and the intensity of treatment<sup>50</sup>, as well as changes in BW and FFM<sup>331</sup> maintain the potential to influence changes in REE measured in patients with cancer.

As previously noted, limited data are available that directly assess the TEF in cancer patients. Yet many studies maintain the assumption that the TEF accounts for 10% of the TEE. Unfortunately, when dealing with the cancer population, this assumption may be violated as conventional treatment regimes may lead to the presence of side effects including mucositis, nausea, vomiting and diarrhoea. The presence of these side effects has the potential to alter food intake and thus TEF. Patients who have undergone a PBST are commonly readmitted to hospital following the procedure due to the presence of mucositis and the need for pain relief. Informal interviews with patients during the treatment period highlighted the adverse effect of treatment on appetite and food intake. This was further supported by the responses to the food frequency questionnaire. The results demonstrated a reduction in the percentage of patients who reported eating more than one serving of each food type assessed, between PI and PII (vegetables: PI=72%, PII=50%; fruit: PI=57%, PII=42%; bread: PI=100%, PII=67%; dairy products: PI=89%, PII=42%; and meat: PI=72%, PII=25%). Fewer patients were also snacking and consuming fluids. The declines were unfortunately greater in food types that yield a higher energy value such as bread, dairy and meat products when compared with food groups yielding a lower energy value, such as vegetables and fruit. The number of patients consuming more than one serving per day of bread, dairy and meat products decreased by 33%, 47% and 47%, respectively. In contrast, the number of subjects consuming more than one serving/day of vegetable and fruit decreased by 22% and 15%, respectively. The observed reduction in the number of servings of food per day would have

implications on both the TEF and energy balance, and be an accounting factor for the decrease in BW observed at PII.

Recommendations have been made for energy intake requirements during treatment. However, given the lack of evidence with regard to changes in TEE as a consequence of treatment, these recommendations are difficult to support. It is crucial to determine how treatment affects TEE, before it is possible to comment on the energy requirements during this treatment period. The results presented by this investigation demonstrate that no significant change in TEE occurs following a PBST. Consequently, the energy intake requirements during the treatment process should also not change.

By PIII, patients in both the control and exercising group demonstrated increases in the number of food servings ingested per day. In the CG, 80%, 40%, 80%, 60%, and 40% of patients ate more than one serving of vegetable, fruit, bread, dairy and meat products, respectively, per day. In contrast, the EG demonstrated a slightly higher percentage of patients eating more than one serving of vegetable, fruit, bread, and dairy products per day (83%, 66%, 88%, and 83%), with the exception of meat product consumption (33%). While the exercising subjects demonstrated a higher serving consumption for the majority of the food groups assessed, this was in conjunction with positive body composition changes, as will be discussed later. It seems evident that participation in an exercise program has a positive result on appetite and energy intake. It also seems plausible to suggest that the elevation in energy intake observed by an increase in the number of servings consumed would lead to an elevation in the TEF, accounting for a small portion of the increase observed in TEE by PIII.

While participation in physical activity may have a positive influence on total energy intake, the type of foods consumed could be improved. In the exercising group, 83% and 67% of subjects consumed less than the Australian daily recommendations for the number of servings for vegetables and fruit<sup>407</sup>. Fifty per cent of patients in the EG also failed to include an appropriate number of bread and cereal product servings per day in their diet, while 84% of patients needed to include a greater number of dairy products. An evaluation of the data collected from the CG provided similar

results. This work supports previous findings which were based on responses to a 'health behaviour and readiness to pursue life-style changes' questionnaire<sup>95</sup>. The results from the survey highlighted that 55% of cancer respondents ate fewer than five daily servings of fruit and vegetables per day<sup>95</sup>, with prostate cancer respondents eating significantly fewer servings when compared with breast cancer patients.

While a correction in EI following treatment is considered important and beneficial for cancer patients, it is crucial to begin to further investigate the influence of long-term changes in EI, in conjunction with EE alterations. A significant increase in EI relative to REE was observed in lung cancer patients at twelve months post-treatment<sup>123</sup>. The elevation in the EI/REE ratio led to a positive energy balance and in turn, an average gain of 3.8kg in FM. Future research should attempt to determine whether EI corrections are matched with EE corrections. The following data on energy expended via physical activity indicates that a correction in TEE is unlikely without any structured intervention.

Although the extent of the data regarding the energy expended on physical activity during or following cancer treatment is limited, a decline in energy spent on this component of TEE has been observed<sup>95, 177</sup>. The PBST hospitalisation period can last up to one month, with patients spending the majority of this time in a supine position. For those patients undergoing more than one transplant, the inpatient period is increased and thus the period of reduced physical activity is further prolonged. During the inpatient period, 'bed' or 'hallway' exercises are needed to maintain the energy spent on physical activity. However, it is not common practice to prescribe exercise to PBST patients in the hospital setting, and unless the patient has an intrinsic motivation to maintain physical activity, energy spent on physical activity during the treatment period is likely to decline. Unfortunately, it could be suggested that many carers and even health professionals see this drop in physical activity as crucial in maintaining an energy balance. When patients are experiencing an 'unwanted' weight loss during treatment, and with participation in physical activity related to an increase in energy expenditure, activity may therefore seem contraindicated. However, evidence provided by this investigation contradicts these beliefs.

The primary aim of implementing an exercise program in the rehabilitation phase of cancer patients is to facilitate recovery and thus allow the patient to perform normal daily activities without undue fatigue. It has previously been reported that TEE is 'robust' and can remain relatively stable when challenged by such stimuli as an exercise intervention<sup>142, 177</sup>. This lack of net TEE change is considered a consequence of one component of TEE compensating for changes in another. For example, given that an exercise intervention causes an increase in the energy spent on physical activity, people may correspondingly decrease the energy spent on daily tasks and spend more time during the day 'resting'. This would be considered an adverse consequence of physical activity in the cancer population given the objective of an exercise intervention. It was identified in this investigation that TEE did not remain stable, but was higher at PIII when compared with PI. These data suggest that the patients were able to maintain their participation in normal daily tasks, in conjunction with expending additional energy during their exercise sessions.

The reduction in BW observed by PII indicated the presence of a negative energy imbalance during the period of PI to PII. Since there was no statistically significant change in TEE during this period and given the mean change was in the negative direction, EI must have substantially decreased between PI and PII. Unfortunately, the significant drop observed in BW ( $p < 0.05$ ) can be characterised by a disproportionate loss of FFM, as indicated by an insignificant loss in FM, in conjunction with a 6% significant decline in FFM ( $p < 0.05$ ). As can be seen in Figures 4.2e, all 7 patients investigated between PI and PII demonstrated a loss of lean tissue. The decline in functional tissue observed in this investigation supports previous findings demonstrating that children between the ages of 1.3-17.1 years experienced an 11% reduction in muscle protein reserves during the first month post-autologous or allogeneic BMT<sup>385</sup>.

A similar disproportionate loss of FFM observed in the PBST patients within this research, has consistently been shown in studies investigating body composition changes in HIV patients<sup>252</sup>. However, evidence within the cancer population is inconsistent. Data derived from the cancer population has shown equal FM and FFM losses<sup>390</sup>, greater FM losses when compared with FFM losses<sup>274</sup> and greater FFM losses when compared with FM losses<sup>177</sup>. FFM losses have also been demonstrated

in patients who are gaining weight<sup>201, 385</sup>. However, of relevance to all findings is that BW changes can be at least partly accounted for by FFM losses, or in simple terms, functional tissue losses. These are the losses that are clinically important to prevent, minimise and/or correct.

Significant improvements in body composition were evident by PIII for the exercise group, with all 6 patients gaining lean tissue. While body weight remained stable between PII and PIII, percentage BF declined ( $p < 0.05$ ) in conjunction with an increase in FFM ( $p < 0.05$ ). The subjects in the EG at PIII maintained an average %BF of  $29.5 \pm 1.6\%$ , and therefore the loss in FM observed by PIII was neither detrimental to their energy reserves or their health. In summary, participation in the exercise program was associated with an elevation in TEE, weight and functional tissue, and a decrease in non-functional tissue. By contrast, the adverse changes in body composition experienced by the patients in the CG as a consequence of treatment were not corrected by three-months post-transplant. The data suggest that unless patients participate in a regular exercise program, body composition will continue to deteriorate and therefore adversely influence functional capacity. This statement can be supported by the failure to regain lost FFM, with a concomitant mean increase in FM observed by PIII in the non-exercising patients. Additionally, 1 out of 5 patients in the control group, assessed at PIII, demonstrated a further loss of functional tissue by 3-months post-transplant. The adverse change in FFM of this subject highlighted the risk for continued declines in functional tissue following treatment cessation.

Investigations involving breast cancer patients have also shown improvements in body composition through the use of an exercise intervention. Breast cancer patients have shown weight stabilisation<sup>226</sup>, and/or %BF improvements in conjunction with increases in FFM, even when BW increases<sup>428</sup>, through participation in aerobic exercise.

The patient population studied in this investigation could be considered as overweight, as shown by BMI (mean = 31.85) or %BF (mean = 27.65) at PI. Therefore, for many patients, a loss in %BF as a consequence of the treatment might be considered beneficial. The continued loss in %BF demonstrated by the EG by

PIII might also be considered advantageous. However, it is a crucial factor for all patients, whether they were classified as overweight or underweight, that a loss of FFM at any stage is detrimental to functional capacity and quality of life. Unfortunately, if body weight changes are the only factor assessed across time, patients, carers and health professionals could falsely perceive the body weight changes as positive. Unless body composition is assessed during the treatment and rehabilitation phases of cancer patients, it is difficult to comment on whether body weight changes are of benefit or detriment to the patient. It is therefore important to begin to find appropriate clinical procedures that can be implemented to assess body composition, rather than just body weight. Consequently, this study assessed body composition via the skinfold technique and deuterium dilution method.

The calculation of %BF via the use of skinfolds was highly correlated with that of deuterium dilution ( $R=0.89$ ,  $p<0.01$ ). Unfortunately, a high correlation does not indicate agreement between the two methods. A significant difference ( $p<0.01$ ) existed between the two assessment techniques, with the skinfold method consistently underestimating %BF when compared with the deuterium dilution method. Since neither of the techniques should be considered more accurate when compared with the other, it could also be said that the deuterium dilution technique consistently overestimated %BF when compared with the skinfold technique. Furthermore, the limits of agreement were calculated between  $-30.26\%$  and  $+21.56\%$ , which is clinically unacceptable. Nevertheless, both techniques are able to detect changes across time, and the value of this information should not be underestimated. While limitations exist for both techniques and either or both of the techniques may not be accurate, they are repeatable and therefore could be used in clinical practice. It seems plausible that the availability and cost associated with the skinfold technique might make its application within the clinical setting more appropriate

#### **4.4.2 Limitations of research and directions for future research**

This investigation provides important information regarding changes in the TEE and body composition of cancer patients across the cancer continuum. However, to confirm the results derived from this investigation, more work is required with

additional subject numbers. Further, research should begin to examine changes in the energy expended on the specific components of TEE including REE, TEF and the energy cost of physical activity. Recommendations for food intake and participation in physical activity during treatment and recovery periods will continue to be limited until more research is performed within the area.

Finally, as previously mentioned, a number of factors such as hydration and potassium concentration changes may influence the accuracy of calculating %BF by using conventional methods. Therefore, further studies are required before %BF calculations derived from techniques such as the use of skinfolds or singly labeled water are considered accurate. Nevertheless the repeatability of these techniques has been demonstrated and therefore, changes in body composition measured by these techniques, either as a result of treatment or an intervention, can be considered accurate.

## **4.5 Conclusion**

Undergoing a PBST led to adverse changes in body weight and fat free mass. While the change in body weight highlighted an energy imbalance during the treatment period, the results of this investigation demonstrated that changes in EI were the likely cause of the imbalance rather than changes in TEE. The adverse changes in body composition associated with the treatment were maintained by the CG during the three month recovery period. In comparison, the EG demonstrated that participation in the regular aerobic and resistance training program led to improvements in body composition, specifically elevations in FFM. Exercise has a functionally important role in preserving and increasing skeletal mass in the rehabilitation phase of cancer patients. The results also indicated that while participation in the exercise program led to a significant increase in TEE, this was not at the expense of lean tissue. Physical activity is an important rehabilitation strategy that can be used to increase the functional tissue of cancer patients following treatment.

# CHAPTER FIVE

## STUDY TWO

### **Changes in aerobic capacity and muscular strength following a PBST and participation in an exercise program**

*“...if patients can sit in a chair, do not let them lie in bed; if they can walk, do not let them sit” Winningham (1991)<sup>425</sup>*

**List of abbreviations specific to Chapter five**

ATP	Adenosine triphosphate
BMT	Bone marrow transplant
BP	Blood pressure
BW	Body weight
CG	Control group
ECG	Electrocardiography
EG	Exercise group
FFM	Fat free mass
HR	Heart rate
MET	Metabolic equivalents
PBST	Peripheral blood stem cell transplant
PI	Phase I
PII	Phase II
PIII	Phase III
RER	Respiratory exchange ratio
SG	Study group
VAS	Visual analogue scale
VE	Ventilation
VO <sub>2</sub> max	Aerobic capacity
WAIT	Winningham aerobic interval training protocol

## **5. Changes in aerobic capacity and muscular strength following a PBST and participation in an exercise program**

---

### **5.0 Introduction**

Cancer, and its associated treatment and sedentary condition, induces a number of adverse physical and functional effects on patients. Interestingly, findings as early as 1978 estimated that at least one third of the functional decline observed in cancer patients, can be attributed to hypokinetic conditions that develop as a result of prolonged inactivity<sup>227</sup>. The adverse physical conditions may include diminished cardiovascular function, reduced lean body tissue and muscular strength, impaired pulmonary function and weight changes<sup>77</sup>. These detrimental changes lead to a reduction in work capacity, and in turn, patients require a greater degree of effort to perform any given task. It is therefore not surprising to find that tiredness and fatigue are associated with performing normal daily activities<sup>105</sup> following cancer treatment.

To avoid fatigue, patients may decrease their level of activity, and thereby induce further muscular and cardiorespiratory losses. Unfortunately, the creation of a self-perpetuating condition of ‘diminished activity which leads to easy fatigability and vice versa’, is not uncommon<sup>105</sup>. General progressive debilitation not only fosters the sense of disability, but also elevates the risk of injury and excessive fatigue for those individuals who attempt physical activity<sup>226</sup>. It is therefore of primary importance to determine the level of physical activity that promotes functional capacity recovery, without the negative consequences of fatigue, muscular weakness and injury<sup>226</sup>.

Of specific relevance to this investigation is the physical status of PBST patients. Reduced physical performance and fatigue constitute universal concerns for BMT patients<sup>101</sup>. Following hospital discharge, the majority of patients find it difficult to undertake normal daily tasks and it may take patients months to years to regain their pre-treatment fitness level<sup>105</sup>. It has been estimated that 40% of BMT patients require a full year for recovery of physical functioning, while approximately 30% of

patients are unable to return to work during the first two years following BMT<sup>105</sup>. In addition, feelings of tiredness, weakness and compromised ability to engage in vigorous physical activity have been reported in 78%, 42% and 76% of patients, respectively<sup>13</sup>.

### 5.0.1 Purpose

Objective 1: To investigate changes between pre- and post-PBST measures of aerobic capacity and muscular strength.

*Research hypothesis for objective 1:*

Aerobic capacity and muscular strength will be adversely affected following a PBST (as determined by pre- and post-transplant measures).

Objective 2: To investigate the role of a three-month duration, moderate intensity, mixed type exercise program on aerobic capacity and muscular strength, post-PBST.

*Research hypothesis for objective 2:*

Exercising PBST patients will demonstrate a faster recovery of aerobic capacity and muscular strength during the three-month post-transplant period, when compared with control patients (as determined by pre- and post-intervention measurement).

## **5.1 Literature Review**

The following review of the literature outlines the cardiovascular, pulmonary and muscular changes that are induced by cancer and its associated treatments, and the role of exercise in correcting these adverse consequences.

Cancer patients are often deconditioned as a result of their surgery and prolonged medical therapy<sup>429</sup>. However, in addition to the adverse changes in aerobic capacity associated with cancer and treatment, is the impact of prolonged inactivity. Inactivity leads to a reduction in the oxidative capacity of skeletal muscle. Consequently, more oxygen is required by deconditioned skeletal muscle for the performance of comparable work, when compared with conditioned muscles, which in turn contributes to fatigue and reduced endurance<sup>227</sup>. Additionally, orthostatic intolerance, ataxia, reduction in stroke rate and increased pulse rate are well documented consequences of prolonged inactivity, influencing aerobic capacity<sup>161</sup>.

Aerobic capacity is influenced by the ability to utilise and metabolise carbohydrates and fats to resynthesise adenosine triphosphate (ATP) for energy. The synthesis of ATP for sustained activity is dependent on oxygen, and thus oxygen uptake and delivery must match the demand of the working muscles. This relies on an effective integrated response of the cardiovascular and pulmonary systems, as well as the oxygen-extraction ability of muscle cells. Disease and treatment have the potential to inhibit the oxygen transport system at any one of several points. However, all points are compromised in a deconditioned state<sup>226</sup>.

A number of side effects from cancer and its associated treatment also maintain the potential to adversely influence pulmonary capacity<sup>241, 413</sup>. Common abnormalities identified by pulmonary function testing include a reduction in inspiratory and expiratory lung volumes such as forced vital capacity, an elevation in arterial carbon dioxide and a reduction in arterial oxygen levels.

Intrapulmonary inflammation may occur as a consequence of radiation, and result in alveolar wall thickening in response to an increased release of surfactant. A further chronic reaction to treatment such as radiation exposure to the lungs, is pulmonary

fibrosis, where the fibrosis may develop as a result of the healing process of pneumonitis. The process of fibrosis consists of collagen replacing the alveolar membrane, thus impairing gas exchange and compliance, with an increase in physiologic dead space. Other pulmonary side effects include pulmonary oedema and respiratory distress, which are potentially caused via changes in capillary permeability and an increase in interstitial lung water<sup>241, 413</sup>. Finally, breathlessness is experienced by approximately 30% of advanced cancer patients, and is often described as the “subjective sensation of an uncomfortable awareness of breathing or difficult breathing”<sup>75</sup>. The effects of breathlessness have the potential to be extensive, adversely influencing quality of life, since they directly impact on the patient’s ability to perform daily activities. Breathlessness can severely limit mobility, while intensifying feelings of anxiety, isolation and fear.

In addition to the cardiovascular and cardiopulmonary effects induced by cancer, treatment and related inactivity, are changes to body composition and muscular strength<sup>121, 161</sup>. Inadequate nutrition and protein intake during cancer treatment have the potential to exacerbate lean tissue losses, while side effects of therapy can contribute to excessive weight gains or losses. Drug therapy such as steroids may lead to myopathy and significant muscle atrophy, and peripheral neuropathies including sensory disturbances and weaknesses may be associated with the use of certain chemotherapeutic drugs such as vincristine and cisplatin. Interruption to nerves or muscles directly from the location of the tumour or alternately during surgical removal of the tumour, may also contribute to muscle strength losses. Finally, one of the earliest and most frequent decrements of inactivity occurs in the musculoskeletal system<sup>121</sup>, with muscle atrophy and decreases in muscular strength and endurance caused by unloading being widely recognised<sup>297, 429</sup>.

Maintenance of adequate muscular performance is an essential consideration for the capacity of individuals to independently perform daily tasks<sup>52</sup>. Every coordinated movement requires the application of muscular force, and the ability to produce this force is reflected by muscular strength. In order to move the body, the muscles must generate enough force to mobilise the bones, with the development of force being dependent on the number of motor units activated, type of motor units activated, initial muscular length upon activation, muscular size, joint angle, and the muscle’s

speed of action<sup>422</sup>. The force that an individual can apply to a task to produce work has also been explained as the ability to generate power<sup>435</sup>. The greater the power generated, the more work able to be performed. As a consequence of muscular impairment due to injury or bed rest, the capacity to generate power is diminished, and is interpreted as 'loss of strength'. It has long been known that significant muscle atrophy and a corresponding loss of strength of approximately 3% per day, can occur within the first week of bed rest<sup>160</sup>. Thereafter, deterioration continues at a rate of strength loss of 1-1.5% per day<sup>245</sup>.

Finally, cancer, treatment and inactivity can influence the physical status of patients through the side effects imposed on mobility. Mobility or flexibility are terms used interchangeably to describe the ability to move a joint through a range of motion and is dependent on the distensibility of the joint capsule, muscle temperature and viscosity, flexibility of ligaments, gender, age, activity level, immobilisation and body type<sup>3, 338</sup>. Mobility contributes to total fitness since maintaining a functional range of motion at all joints of the musculoskeletal system is important to efficient body movement<sup>5</sup>.

Compression of a nerve plexus or peripheral nerves, or interruption to the neuromuscular system as a result of cancer or certain treatment regimens, may adversely affect range of motion and thus the ability to perform daily activities<sup>161</sup>. For example, increased stiffness in periarticular structures and a reduction in cartilage integrity are likely to occur when a patient undergoes prolonged rest in a cast. Radiotherapy, or radiotherapy in conjunction with chemotherapy maintains the potential to contribute to the presence of joint contractures. Additionally, patients who experience pain in certain positions may try to assume the most comfortable position. In turn, this may foster the development of flexion contractures and adversely affect range of motion.

Inactivity can further exacerbate range of motion limitations caused by cancer and treatment. With prolonged inactivity, joint mobility is reduced by an increase in the density of supportive collagen tissues surrounding the joint<sup>428</sup>. Contractures caused by the shortening of soft tissue structures surrounding a joint, in association with weakened muscles, further minimise flexibility<sup>226</sup>.

### 5.1.1 Physical status of cancer patients

Evidence supports the notion that cancer diagnosis, treatment and inactivity lead to a reduction in aerobic capacity and muscular strength. The initial exercise capacity of the cancer patient is within a range of 3-6 metabolic equivalents (MET) (i.e. 10.5-20.5 ml/kg/min)<sup>3</sup>. This range was derived from investigations assessing patients with breast cancer who had undertaken conventional treatment regimens. However, more recent published work investigating BMT patients, has shown that the initial exercise capacity of patients being treated with more intensive regimes also falls within this range. Maximal MET values of  $4.7 \pm 1.2$  were reported on average 30 days following a BMT procedure<sup>101</sup>.

While few studies exist that have assessed physical status immediately following cancer treatment, information regarding the cardiovascular and musculoskeletal status of patients can be found in work assessing patients who are considered long-term survivors of cancer. Forty-three per cent of patients who had received anthracycline therapy for acute lymphoblastic leukaemia (ALL) demonstrated abnormalities during exercise testing which limited their stamina<sup>175</sup>. Twenty-five per cent and thirty-one per cent of long-term survivors (1.5-16 years) of acute leukaemia failed to attain normal maximal aerobic capacity, and normal anaerobic threshold, respectively<sup>38</sup>. An earlier investigation also found that children treated for ALL have a reduced maximal exercise capacity<sup>180</sup>, with the etiology of the results thought to be a combination of the effect of treatment modalities and low participation rates in physical activity. Moreover, psychological testing demonstrated that children treated for leukaemia perceive their exercise capacity as limited and therefore avoid exercise participation<sup>58</sup>.

Musculoskeletal disorders and gross motor disabilities have also been reported in children with ALL<sup>440</sup>. While the majority of children were able to perform basic motor skills, their levels of gross motor proficiency and performance on selected measures of musculoskeletal function were significantly poorer than those of school-matched peers. In addition, reduced muscle strength, weakness and progressive osteopenia relating to poorer bone integrity was further identified.

Limited research involving long-term survivors of patients who have undergone a BMT exists. Sixty-three patients who had undergone a BMT, aged 18 years or less, were assessed to determine cardiac function and the prevalence of cardiac abnormalities, at one year post-transplant<sup>109</sup>. Forty-one per cent of patients had a cardiac abnormality with 21 out of 26 patients demonstrating the abnormality pre-transplant. Furthermore, 16.4% showed abnormal resting electrocardiographs, three patients illustrated decreased left ventricular ejection fraction, and 23 out of 31 patients who underwent an exercise test demonstrated a borderline or abnormal response.

More recently, a long-term follow-up study assessing cardiopulmonary function and recovery was performed on 33 patients who had undergone a BMT between 1979 and 1994<sup>166</sup>. While no significant episodes of arrhythmia or electrocardiographic evidence of ischaemia occurred during exercise testing, maximal cardiac index failed to improve over a median follow-up time of six years following BMT. This finding is indicative of a persistent impairment of the cardiovascular response to the metabolic demand of exercise. Subclinical cardiac dysfunction was also evident as a result of the combination of a low cardiac index and a normal peak HR, which demonstrated a low stroke volume. Although cardiovascular function was impaired, there was no deterioration over time. In turn, this suggested that the myocardial injury following BMT is persistent, but not progressive. Additionally, aerobic capacity via the measurement of oxygen consumption at peak exercise and at the ventilatory threshold was assessed. The study confirmed that both maximal aerobic capacity and aerobic capacity at ventilatory threshold were decreased in BMT patients, when compared with age- and sex-matched healthy controls. The aerobic capacity at ventilatory threshold also failed to improve across the study period, indicating impaired oxygen delivery.

In summary, the above research shows that patients who have been treated with either conventional or intensive regimens report substandard physical and psychosocial status. Therefore, given that BMT patients often undertake conventional treatment options prior to the transplant, it is possible that their poor post-BMT status is a function of previous treatment rather than the BMT.

Unfortunately, information regarding the physical status of BMT recipients prior to BMT is limited<sup>14</sup>. Consequently, this also influences the ability to determine the exact impact of the BMT on physical status. To investigate this issue a prospective study assessed 28 adult BMT recipients prior to BMT and then again at 12-16 months post-BMT<sup>14</sup>. Comparisons of mean scores for various physical and psychosocial status indices demonstrated few significant differences between pre- and twelve month post-BMT scores. However, this was based on group findings and when individual results were considered, it became evident that many patients were unable to return to pre-BMT levels within the twelve-month period. The individual findings were of particular relevance to the older patients, indicating that the older the patient, the poorer post-BMT status.

Research findings clearly demonstrate that the physical status of patients with cancer is adversely affected following conventional treatment or intensive treatment such as a BMT. Additionally, patients may remain at lower than 'normal' functioning levels for many years post-treatment. Bone marrow transplant patients are at risk of experiencing poor physical status prior to the BMT regimen, potentially due to the conventional treatment already undertaken.

### **5.1.2 Fatigue**

The cardiorespiratory and musculoskeletal losses observed as a consequence of cancer, treatment and inactivity, have been regarded as substantial contributors<sup>430</sup>, if not the primary causes<sup>104</sup> of other common side effects, such as fatigue. Fatigue is one of the most common and pervasive physiological consequences associated with cancer, and is reported in 40-100% of patients<sup>343</sup>. For certain diagnoses, 30-40% of patients may experience fatigue for years following treatment cessation<sup>367</sup>. While the advent of new antiemetic regimens has advanced the management of symptoms such as nausea and vomiting, fatigue is one symptom that remains difficult to manage<sup>315</sup>.

Fatigue can be described as being multifactorial and multidimensional<sup>318</sup>. There are biological, psychological, social and personal factors that have the potential to influence the onset, impact, expression, duration and severity of cancer-related fatigue<sup>318</sup>. Other potential fatigue mechanisms have been reported and include sleep

disturbances, biochemical changes secondary to disease and treatment, internal and external environmental conditions, activity levels, nutritional status and diverse inherent factors<sup>430</sup>. Fatigue can be initiated by radiation, surgery and chemotherapy, may increase over the course of treatment, and persist for months afterwards.

Treatment-related fatigue is severe for many patients and imposes limitations on the ability to perform normal daily tasks<sup>105</sup>. Patients note that cancer treatment-related fatigue is very different from the fatigue often experienced prior to cancer diagnosis, as it is more intense, chronic, disruptive, and is unrelieved with rest<sup>342</sup>. With the aim of reducing fatigue, physical activity levels are often down-regulated and the detrimental cycle of 'diminished activity which leads to easy fatigability and vice versa' is initiated<sup>105</sup>. Eighty-four per cent of patients experiencing fatigue used resting and napping as a mechanism to overcome fatigue. However, one of the few tested interventions that has reliably demonstrated the ability to reduce fatigue levels in cancer patients is exercise<sup>246</sup>.

### **5.1.3 Aerobic exercise and cancer patients**

Given the low maximal METS experienced by patients following treatment, it is not surprising that participating in normal daily activities including walking, preparing meals, vacuuming and mowing, that have calculated MET values between 2.5-4.5<sup>7</sup>, rapidly induce fatigue. These activities would require patients to work between 50-100% of their maximal aerobic capacity. It therefore seems evident that if a patient's maximal aerobic capacity could be enhanced, their ability to function throughout the day would improve, and in turn quality of life would be positively influenced. Aerobic exercises including walking, cycling, swimming or any activity that uses large muscle groups have the potential to improve the oxidative capacity of skeletal muscles, stimulate the general adaptation of the aerobic biochemical system, and result in measurable increments of oxygen uptake<sup>227</sup>.

#### **5.1.3.1 Aerobic exercise studies**

Exercising cancer patients have demonstrated improved work capacities, lower HR at a given power, increased maximum workloads and lengthened time to achieve peak

aerobic capacity (peak  $\text{VO}_2$ ) when compared with non-exercising patient controls<sup>226, 227</sup>. Winningham and MacVicar (1988)<sup>427</sup> further reported that exercising breast cancer patients demonstrated a 40% improvement in functional capacity after participating in a Winningham Aerobic Interval Training (WAIT) protocol, when compared with no significant change in the control and placebo groups. Additionally, following a ten week aerobic exercise intervention, patients with breast cancer experienced a 20.7% increase in  $\text{VO}_2$  (1.37 - 1.73 L/ $\text{O}_2$ ), compared with a 1.8% reduction in peak  $\text{VO}_2$  (1.11 - 1.09 L/ $\text{O}_2$ ) reported in non-exercising patients<sup>226</sup>. The exercising cancer patients were also able to make comparable gains in functional capacity when compared with healthy age-matched exercising controls (where functional capacity increased by 17.4%).

Mock and coworkers (1997)<sup>247</sup> implemented a self-paced, progressive (20-30 minutes) walking program for the duration of radiation treatment in breast cancer patients. Outcome measures evaluated included physical functioning (as assessed by the 12-minute walk test) and fatigue, anxiety, depression and difficulty sleeping. Eighty-six per cent of the experimental group maintained the active exercise program for the duration of the study. The exercise group was able to increase distance walked by 4% following treatment cessation, in contrast to the 5% decline demonstrated by the control group. While all participants reported fatigue as the most intense symptom, the exercise group experienced significantly lower levels of fatigue. Two of the most important findings derived from this research was that a self-paced walking program was tolerated by breast cancer patients, and that higher walking activity levels correlated with higher physical performance scores<sup>246</sup>.

A similar study involving women being treated for breast cancer provided supporting evidence<sup>343</sup>. The intervention tested involved an eight week, home-based, low-to-moderate intensity exercise program that allowed for a recovery period, and that accommodated individual cycles of chemotherapy by reducing the duration of exercise. Subjects were able to participate in any aerobic activity of their choice, given the exercise frequency was maintained at three to four times per week, for duration of 15-30 minutes. Participants who adopted the exercise program demonstrated a 10.4% increase in functional capacity as measured by the 12-minute walk test. In contrast, nonexercisers showed a 16% decline. Those women who

regularly exercised experienced less fatigue and increased vigour, in comparison to those women who did not exercise. However, it is important to note that this research also demonstrated a U-shaped relationship between high intensity and fatigue, whereby both nonexercisers and high-intensity or long-duration exercisers, reported elevated fatigue levels, in comparison to 'moderate' exercisers.

Five patients diagnosed with varying cancers and having undergone different treatment regimens, were recruited into an exercise intervention program on the basis of suffering from severe fatigue<sup>103</sup>. Fatigue for all five patients imposed significant limitations on daily activities, causing one patient to forgo school and another to leave university. The exercise intervention program implemented consisted of aerobic training on a treadmill for a period of six weeks, at an intensity relating to  $80\pm 5\%$  of maximum HR. Prior to participation in the study, these patients had been advised to seek periods of rest and to reduce their level of activity, in order to reduce their fatigue. The results of the investigation concluded that these well-meaning recommendations had worked paradoxically. Exercise could interrupt the detrimental cycle of lack of exercise, impaired performance and easy fatigability. By the end of the training program, subjects experienced improved physical performance as measured by distance walked, maximal METs, and HR and lactate levels at submaximal workloads. Feelings of fatigue also improved with two patients resuming studies, and the others able to participate in daily tasks without undue fatigue.

Fourteen out of twenty patients undergoing either an allogeneic or autologous BMT were able to complete a six-week walking program<sup>101</sup>. By the end of the training period, physical performance had increased for all fourteen patients, as was measured by training speed, maximal walking distance, maximal performance (measured via METs and km/hour walked), HR and lactate. Of clinical importance was the finding that all patients reached MET values high enough to perform tasks of daily living (as was classified as 5 METs). The researchers commented that these physical gains led to improvements in emotional stability as was observed through an elevation in self-confidence and reductions in depressed states. Additionally, no complications attributable to the training program occurred. Unfortunately, the interpretation of results was limited by the absence of a control group, and comments made on

emotional stability were subjective and not quantified via questionnaires. The investigation however, provided evidence illustrating that BMT patients can show improvements in functional capacity within weeks of discharge from the BMT unit.

Promising results were also shown in an exercise intervention investigation performed with autologous BMT patients. Patients in the exercise group exhibited significant improvements in maximal performance following the completion of a six week, daily walking program, at 90% HR<sub>max</sub><sup>104</sup>. In contrast, 19% and 25% of the control group failed to show any improvements and were unable to reach MET values sufficient to perform daily activities, respectively. Additionally, 25% of the control group reported fatigue at the conclusion of the study and reported limitations in performing usual activities. These limitations were of no concern to the experimental group and only 6% of the exercise group failed to attain the minimum MET value.

Finally, improvements in haemoglobin concentration, functional capacity, duration of neutropenia and thrombocytopenia, severity of diarrhoea and pain, and duration of hospitalisation have also been shown in exercising BMT patients<sup>80, 102, 104</sup>.

#### **5.1.4 Strength training and cancer patients**

While exercise intervention studies in cancer are relatively scarce, within the available studies, aerobic exercise has been given much of the attention. It is important to highlight that daily living activities repeatedly involve both isometric and isodynamic exercise<sup>404</sup>. Therefore, it seems unreasonable to exclude resistance training from exercise programs prescribed for cancer patients. To date, no research could be identified that has implemented a resistance training program in the cancer population. Strength training prescription will therefore continue to be limited until such data are available. Pending further research, data from strength training intervention studies with other clinical populations may provide some insight to the potential benefits that participation in a strength training program could provide.

#### 5.1.4.1 Strength training studies

Improvements in muscular strength have been universally reported, following low to moderate isotonic, isokinetic and circuit resistive exercise training in the young, middle-aged, older individuals, and cardiac populations<sup>404</sup>. Studies performed with the 'healthy' population have shown that strength training maintains the potential to produce upper and lower body strength gains in the range of 20-50%, while studies recruiting the older population and cardiac population have demonstrated strength improvements between 9-227% and 20-40%, respectively<sup>404</sup>. The wide range of strength gains is largely dependent upon the muscle groups studied and initial strength levels<sup>404</sup>.

Assessing strength training intervention studies utilising HIV patients may provide slightly more relevant information regarding the potential role of strength training for patients with cancer. An investigation with HIV-patients was conducted to study the effects on body composition of an anabolic steroid treatment in conjunction with a resistive exercise program. All study participants received the drug and were randomly assigned into either a progressive resistance exercise group or control group. The results showed that by the end of the first month, six control subjects gained 1.9% of entry weight, one subject lost weight, and two lost body cell mass. In contrast, seven subjects in the exercise group demonstrated a 3.2% increase of entry weight and no exercising subject demonstrated a body weight decline<sup>323</sup>. In another HIV-1 study, significant gains were observed in muscular strength for the regions of the legs, chest, shoulder and arms following a six-week progressive resistance training program<sup>370</sup>. These patients at post-program experienced significantly higher levels of muscular strength when compared with the control group. Those in the control group, who performed no exercise during the six-week period, either showed no increase in muscle strength, or in some cases demonstrated losses. In addition, body weight and girth measures increased for the experimental group, while the control group showed significant decreases for these same variables.

Improved cardiovascular and anthropometrical status has been shown in HIV-1 and AIDS patients following participation in both aerobic and strength exercises<sup>320</sup>. The experimental group participants demonstrated a 30% and 17% improvement in

muscular strength and cardiovascular and cardiorespiratory fitness (as measured by  $\text{VO}_2$  peak), respectively, following a twelve-week program. In contrast, no changes were observed in the control participants for these measures.

Lastly, an investigation studying the effects of an aerobic only, a strength training program only and a stretching control group on body composition and fitness was undertaken on HIV-1 males and demonstrated supporting evidence for the above studies<sup>222</sup>. It was found that the aerobic-only group demonstrated the highest fitness changes, while the strength training group demonstrated the highest muscular strength gains. Both groups demonstrated losses in fat mass and gains in fat free mass, with the aerobic group illustrating the higher fat mass losses and the strength group higher fat free mass gains. While these results demonstrated the principle of training specificity, the results further illustrated that a certain level of 'crossover' can occur. Those in the aerobic group showed partial improvements in leg strength, and the weight training group showed partial improvements in cardiovascular fitness. Importantly, the results also demonstrated that inactivity is associated with physiological declines, as was evidenced by the decline in fitness and muscular strength seen in the control group.

In summary, the results of the investigations involving HIV patients provide important evidence that supports the use of strength training to be used to correct or combat the wasting process of lean tissue, and thus the reduction in muscular strength, associated with disease and treatment.

## 5.2 Methodology

Chapter 3 provided a detailed outline of the methodological procedures that relate to subject recruitment, the testing phases and the intervention program implemented. In summary, twelve patients, with six patients in each group were recruited. Of these, seven patients were recruited at PI, while the remaining subjects entered the investigation at PII. Outlined below are the methodological procedures that relate specifically to the aims of this section of the investigation and involve cardiorespiratory and muscular strength measures.

### 5.2.1 Cardiorespiratory assessment

Maximum oxygen consumption ( $\text{VO}_2$  max) was assessed via a maximal graded treadmill exercise test (GXT). Originally, a testing protocol starting at a walking speed of 2.5 km/h and a grade of 5%, with increments in speed and grade every two minutes was planned. However, on presentation of the subjects during the treadmill familiarisation session, it became clear that while this protocol was appropriate for some patients, for others it was either 'too hard' or 'too easy'. If this protocol were employed, some patients would have completed the test within five minutes while others would have required up to twenty minutes. It has been previously shown that incremental tests between 8-17 minutes are optimal when trying to measure  $\text{VO}_2$  max<sup>55</sup>. In order to ensure patients reached their  $\text{VO}_2$  max within this time span, it was evident that the treadmill protocol needed to be individually designed. Therefore, the treadmill speed began at a slower than 'normal' or 'comfortable' pace for each subject. The initial workload was set at a speed ranging between 1-4 km/h and a grade of 0. Depending on HR and the Visual Analogue Scale (VAS) response, workload was increased every 1-2 minutes through the use of speed and/or grade. Details of the VAS have been provided in Appendix VI.

For several patients (particularly those in the exercising group), a variation of the graded exercise test protocol employed at PI and PII was usually required for  $\text{VO}_2$  max assessment at PIII. This prevented comparison of HR and VAS at specific workloads, however it ensured that the time to reach  $\text{VO}_2$  max was similar for all three testing phases.

Due to the predicted reduced fitness level of the patients and the lack of regular exercise participation during the prior months, only lower body stretches were performed during the warm-up. This was instead of the more common warm-up which involves a combination of aerobic exercise and stretching. For some patients, walking at the slowest available treadmill speed could induce fatigue. Therefore, to ensure that the patient was not fatigued prior to the test, and to maximise the ability to reach  $\text{VO}_2$  max within the time period allocated, no warm-up was performed on the treadmill. Variables assessed throughout the test included gas analysis, electrocardiography (ECG), HR, blood pressure and the VAS.

A Quinton treadmill (Q65 Series 90), electrocardiogram (ECG – Q4500) and gas analysis machine (Q-Plex 1) were used to measure ECG, ventilation (VE),  $\text{VO}_2$  (ml/kg/min), and the respiratory exchange ratio (RER). To configure the Q4500 for a GXT, an exercise test environment including the procedure and protocol to be implemented was established. Patient data and room conditions including dry temperature, barometric pressure, humidity and syringe volume (3L) were then entered and used for the calibration procedures. The Q-Plex 1 was calibrated using both high-cal ( $\text{CO}_2$ ,  $4.987 \pm 0.020\%$  &  $\text{O}_2$ ,  $18.14 \pm 0.02\%$  in Nitrogen) and low-cal ( $\text{CO}_2$ ,  $3.986 \pm 0.020\%$  &  $\text{O}_2$ ,  $16.69 \pm 0.02\%$  in Nitrogen) gas ranges and the volume and flow rates were calibrated with the use of a 3L calibration syringe (Hans Rudolf Inc. Model No. 5530). Following calibration, the patient was then prepared for the exercise test.

During the familiarisation session, and once again prior to subject preparation for the exercise test, a thorough explanation of the testing procedure was given to the patient. At this time, the patient was also given instructions on how to assess their perceived effort using the VAS. Once the patient understood the process they were prepared for the testing procedure. This included preparation and placement of electrodes for ECG, followed by preparation for gas analysis and blood pressure (BP) assessment. Preparation for gas analysis involved attachment of the nose clip, mouthpiece and appropriate headgear. Finally, the sphygmomanometer cuff was applied to the left arm in order to assess BP. In addition to the use of the VAS, the

patient was instructed to use hand signals including the ‘thumbs up’ or thumbs down’ signal, to communicate feelings during the testing procedure.

Medical supervision was present at all testing sessions, and ECG was continually monitored throughout the testing protocol. HR was measured and recorded every minute, while BP and VAS were assessed every two minutes. During the final stages of the test, a more regular assessment (every 30 seconds) of the VAS was performed.

VO<sub>2</sub> max is classically defined as the greatest amount of oxygen that can be utilised under the most exhaustive exercise, and is traditionally measured as the point where oxygen consumption levels off even when work rates continue to rise. However, this measurement endpoint, known as plateauing, is no longer universally accepted for a number of reasons mentioned throughout the literature<sup>302</sup>. Plateauing is also difficult to reproduce and is highly dependent on sampling methods. Therefore, several investigators have referred to the highest oxygen consumption attained for a given presumed maximum exercise effort as peak VO<sub>2</sub>. The following criteria were implemented within this study to determine test cessation and peak VO<sub>2</sub>:

- when VO<sub>2</sub> reaches a plateau, that is, a rise in oxygen uptake of less than 0.15L.min<sup>-1</sup> or less than 2ml.kg<sup>-1</sup>.min<sup>-1</sup> with an increase in power output
- if the subject grabs the handrails and is unable to maintain work output
- when the subject scores 10 on the VAS
- if the subject feels dizzy, has an unsteady gait, or expresses unusual sensations of discomfort
- if the RER is greater than 1.1
- loss of ECG monitoring or the occurrence of any serious ECG abnormality
- if systolic BP (SBP) is greater than 250mmHg and/or diastolic BP is greater than 120 mm/Hg
- if SBP falls greater than 20mmHg with increased power output.

On presentation of any of these criteria, the treadmill speed was reduced to a comfortable speed as judged by the patient, at a 0% grade. The nose clip and mouthpiece were removed, however continual recordings of HR, BP and ECG occurred until HR was below 100bpm. Peak VO<sub>2</sub> was measured in ml/kg/min, and body weight (BW) and fat free mass (FFM) levels evaluated in Chapter 4 were used to express peak VO<sub>2</sub> in L/min, and ml/FFM/min.

## 5.2.2 Muscular strength assessment

The strength measures were selected for this study on the basis of their relationship to normal functional tasks. It was concluded that both isometric and isodynamic assessments should be used since they are utilised repeatedly during daily tasks. Therefore, the following tests were implemented to assess muscular strength:

- an isometric handgrip strength test – the prevalence of isometric tasks is greater for the hand than for any other biomechanical component<sup>435</sup>, and is associated with tasks such as opening jars and bottles and turning on tight taps;
- 15 repetition maximum (RM) bench press – which assesses general upper body strength; and
- 15RM leg press test – which assesses general lower body strength.

Strength usually refers to a maximum single muscular contraction and is sometimes assessed via a 1RM. However, assessing 1RM on a population which has experienced excessive strength losses or who may be at risk of low skeletal strength due to side effects of the disease and its associated treatment, may be contraindicated. When more than one contraction can be performed against a specific resistance, pure strength is no longer being assessed<sup>338</sup>. However, an individual maintains good muscular strength when they possess good high resistive endurance<sup>338</sup>. For this reason, assessing a 15RM has been regarded as a muscular strength test since an indication of strength status is provided. By having subjects use the greatest resistance possible to complete 15 repetitions, a low-repetition and high-resistance regimen was avoided and the risk of musculoskeletal injury reduced. The specific procedures implemented for the muscular strength tests are presented in Appendix VII.

## 5.2.3 Statistical analysis

Data for the peak ventilation, peak aerobic capacity, peak HR, peak RER and muscular strength were collected at each of the three testing phases and were analysed according to the statistical procedures outlined in Chapter 3.

Strength results were adjusted for changes in FFM as a consequence of the following statistical procedures. When strength values were correlated with FFM, a significant ( $p < 0.05$  for BP & HGR, and  $p < 0.01$  for LP) positive correlation ( $r = 0.402$  – BP;  $0.372$  – HGR;  $0.505$  – LP) was identified. Since the FFM of the subjects tested altered across the 3 testing phases, it was deemed crucial to appropriately adjust strength results with regard to these FFM fluctuations. Fat free mass changes across time were appropriately adjusted by dividing upper body (BP) and lower body (LP) strength values by FFM values. However, when this calculation was performed with handgrip (HGR) strength values, a second negative ( $R = -0.369$ ,  $p < 0.05$ ) correlation for HGR/FFM and FFM was identified. In order to find an appropriate method of adjusting for FFM changes, HGR strength values and FFM values were log-transformed and analysed by a linear regression<sup>91</sup>. The linear regression coefficient was  $0.761$  and the standard error was  $0.194$ . The coefficient in this case is the power to which FFM must be raised to completely adjust HGR for FFM. It should be noted that the coefficient was within 2 standard errors of either  $0.5$  or  $1$ , demonstrating that the data can be adjusted by either dividing by FFM, which is in effect  $FFM^1$ , or dividing by  $FFM^{(0.5)}$ . Given the data had already been calculated by dividing by FFM, results for HGR strength values were expressed as a ratio of FFM.

### 5.3 Results

Although 7 subjects were recruited at PI, equipment problems during one patient's testing session reduced the accuracy of the aerobic capacity data collected and the data was therefore not included in the analysis. As shown in Table 5.1, mean values for peak ventilation, aerobic capacity and strength were reduced following the transplant. However, differences between pre- and post-transplant data were only significant ( $p < 0.05$ ) for upper body strength. No change was evident in the mean peak HR and RER attained during the GXT tests.

**Table 5.1** Aerobic capacity and strength measures at PI and PII for the study group (mean±SE)

SG Variable	PI		PII		p value
	Mean	SE	Mean	SE	
Peak VE (L/min)	71.15	3.90	71.48	2.44	0.943
Peak VO <sub>2</sub> (L/min)	1.97	0.13	1.73	0.08	0.135
Peak VO <sub>2</sub> (ml/kg/min)	23.71	1.25	21.76	0.79	0.211
Peak VO <sub>2</sub> (ml/FFM/min)	35.85	2.40	33.20	1.50	0.367
Peak HR (b/min)	165	3	164	2	0.725
Peak RER	1.09	0.04	1.10	0.02	0.564
Handgrip strength (Handgrip Right (units)/FFM(kg))	0.81	0.07	0.76	0.05	0.47
Upper body strength (log [Bench Press (kg)/FFM(kg)])	-0.46	0.06	-0.61	0.04	0.049*
Lower body strength (Leg Press (kg)/FFM(kg))	1.17	0.08	1.06	0.06	0.450

n = 6 at PI for VE, VO<sub>2</sub>, HR and RER data, and 7 at PI for strength data; n = 12 at PII

\*  $p < 0.05$

The control group showed little change in peak ventilation, peak aerobic capacity and muscular strength across the three testing phases (Table 5.2). Only the change identified for peak aerobic capacity (L/min), between pre- and post-transplant, was significant.

**Table 5.2** Aerobic capacity and strength measures across the testing phases for the control group (mean±SE)

Variable	Phase	Mean	SE	Comparison	p value
Peak VE (L/min)	I	62.22	5.55	PI - PII	0.697
	II	64.15	3.46	PI- PIII	0.954
	III	61.91	3.97	PII - PIII	0.578
Peak VO <sub>2</sub> (L/min)	I	1.76	0.19	PI - PII	0.042*
	II	1.44	0.16	PI- PIII	0.182
	III	1.56	0.13	PII - PIII	0.290
Peak VO <sub>2</sub> (ml/kg/min)	I	23.68	1.79	PI - PII	0.090
	II	20.13	1.11	PI- PIII	0.304
	III	21.53	1.28	PII - PIII	0.359
Peak VO <sub>2</sub> (ml/FFM/min)	I	35.68	3.42	PI - PII	0.147
	II	29.85	2.13	PI- PIII	0.397
	III	32.23	2.44	PII - PIII	0.431
Peak HR (b/min)	I	158	4	PI - PII	0.509
	II	155	3	PI- PIII	0.816
	III	157	3	PII - PIII	0.606
Peak RER	I	1.05	0.05	PI - PII	0.383
	II	1.10	0.03	PI- PIII	0.211
	III	1.15	0.04	PII - PIII	0.105
Handgrip strength	I	0.86	0.08	PI - PII	0.625
Handgrip right	II	0.79	0.05	PI- PIII	0.319
(units)/FFM(kg)	III	0.72	0.06	PII - PIII	0.442
Upper body strength	I	-0.43	0.09	PI - PII	0.178
log [Bench press	II	-0.61	0.06	PI- PIII	0.245
(kg)/FFM(kg)]	III	-0.59	0.06	PII - PIII	0.882
Lower body strength	I	1.21	0.16	PI - PII	0.464
Leg press (kg)/FFM(kg)	II	1.03	0.10	PI- PIII	0.401
	III	0.98	0.12	PII - PIII	0.812

n = PI – 3, PII – 6, PIII - 5

\* p&lt;0.05

The trend for change was similar for all measures assessed in the exercising group (Table 5.3), and demonstrated that participation in an exercise program led to significant improvements in peak ventilation ( $p<0.01$ ), peak aerobic capacity ( $p<0.05$ ) and upper and lower body strength ( $p<0.01$ ). Additionally, results recorded following the 3-month intervention period were significantly higher than pre-treatment levels, for peak aerobic capacity (L/min,  $p<0.05$  and ml/kg/min,  $p<0.01$ ) and lower body strength ( $p<0.01$ ).

**Table 5.3** Aerobic capacity and strength measures across the testing phases for the exercise group (mean±SE)

Variable	Phase	Mean	SE	Comparison	p value
Peak VE (L/min)	I	80.08	5.47	PI - PII	0.874
	II	78.82	3.46	PI- PIII	0.012*
	III	105.82	3.46	PII - PIII	0.002**
Peak VO <sub>2</sub> (L/min)	I	2.19	0.18	PI - PII	0.557
	II	2.02	0.16	PI- PIII	0.034*
	III	2.90	0.16	PII - PIII	0.004**
Peak VO <sub>2</sub> (ml/kg/min)	I	23.73	1.76	PI - PII	0.885
	II	23.38	1.11	PI- PIII	0.007**
	III	32.55	1.11	PII - PIII	0.001**
Peak VO <sub>2</sub> (ml/FFM/min)	I	36.03	3.37	PI - PII	0.908
	II	36.55	2.13	PI- PIII	0.051
	III	46.37	2.13	PII - PIII	0.021*
Peak HR (b/min)	I	172	4	PI - PII	0.884
	II	173	3	PI- PIII	0.808
	III	174	3	PII - PIII	0.898
Peak RER	I	1.12	0.04	PI - PII	0.767
	II	1.10	0.03	PI- PIII	0.417
	III	1.15	0.03	PII - PIII	0.683
Handgrip strength	I	0.75	0.07	PI - PII	0.621
Handgrip right (units)/FFM(kg)	II	0.72	0.05	PI- PIII	0.875
	III	0.76	0.05	PII – PIII	0.450
Upper body strength	I	-0.49	0.17	PI – PII	0.181
log [Bench press (kg)/FFM(kg)]	II	-0.61	0.06	PI – PIII	0.068
	III	-0.32	0.06	PII – PIII	0.003**
Lower body strength	I	1.12	0.13	PI – PII	0.897
Leg press (kg)/FFM(kg)	II	1.10	0.10	PI- PIII	0.001**
	III	1.81	0.10	PII – PIII	0.000**

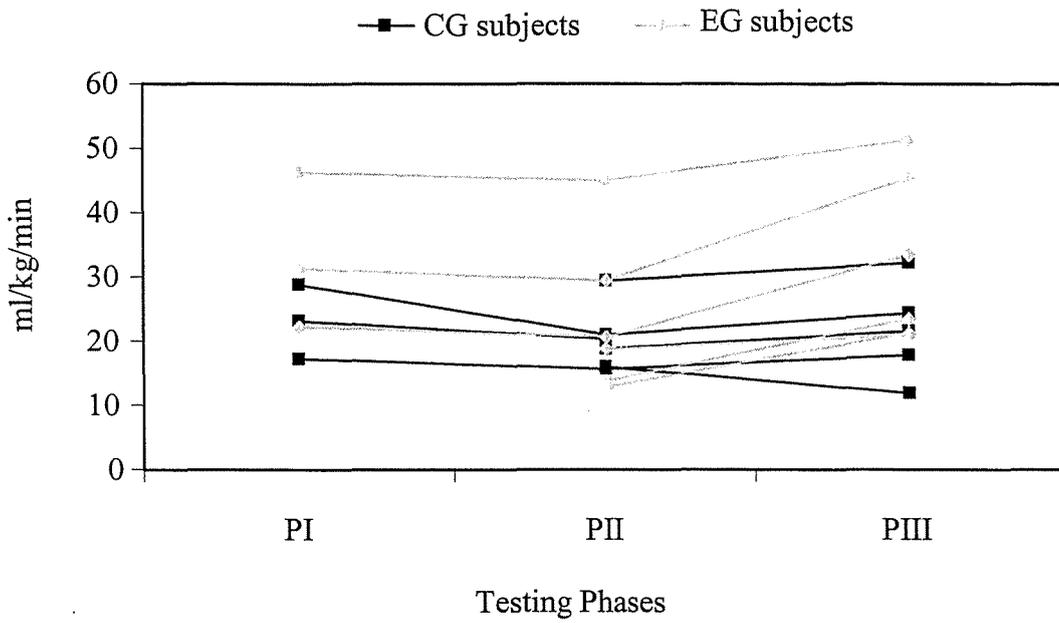
n = PI – 3, PII – 6, PIII - 6

\* p&lt;0.05, \*\* p&lt;0.01

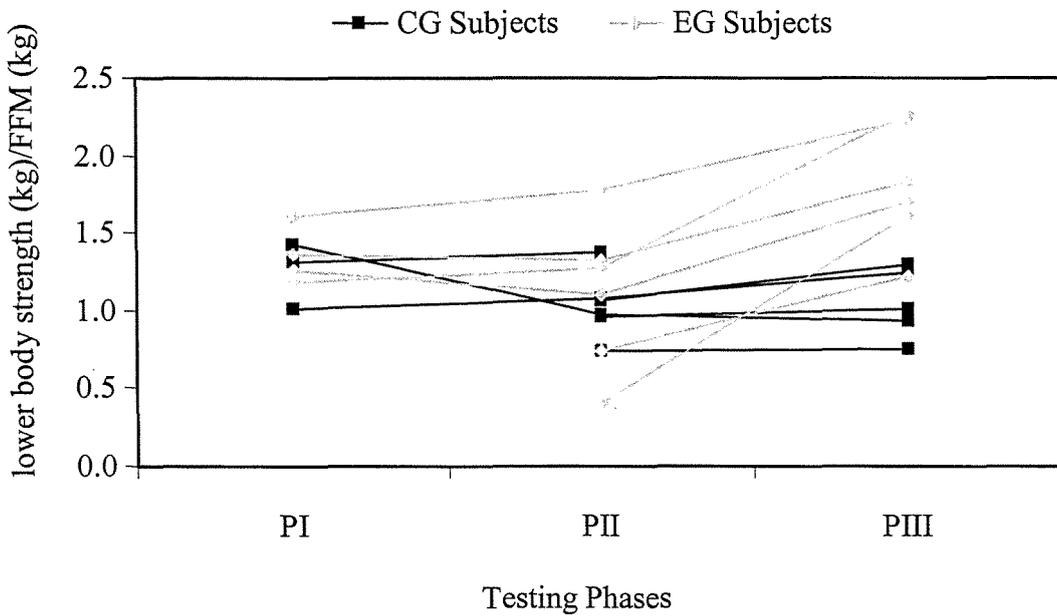
Figure 5.3a and b displays individual changes in aerobic capacity (ml/kg/min) and muscular strength (lower body strength adjusted for FFM changes) across the testing phases, for subjects in the control and exercise group. With the exception of 1 subject, the pattern and magnitude of change was similar for all subjects in these measures between PI and PII. By 3-months post-transplant, greater gains in aerobic capacity and muscular strength were evident in all 6 patients participating in the intervention program, when compared with the 5 subjects in the control group. In addition, all exercising subjects showed improvements, while subjects within the control group displayed slight mean gains, no change or mean losses in these measures.

**Figure 5.3** Individual changes in peak aerobic capacity and lower body strength across the testing phases (PI, PII and PIII)

**(a)** Peak aerobic capacity



**(b)** Lower body strength



As shown in Table 5.4, following the 3-month intervention period, the exercising patients recorded higher mean fitness and strength values than the patients in the control group, with the differences between peak ventilation ( $p<0.05$ ) and lower body strength ( $p<0.01$ ) being significant.

**Table 5.4** Aerobic capacity and strength measures at PIII for the control and exercise group (mean $\pm$ SE)

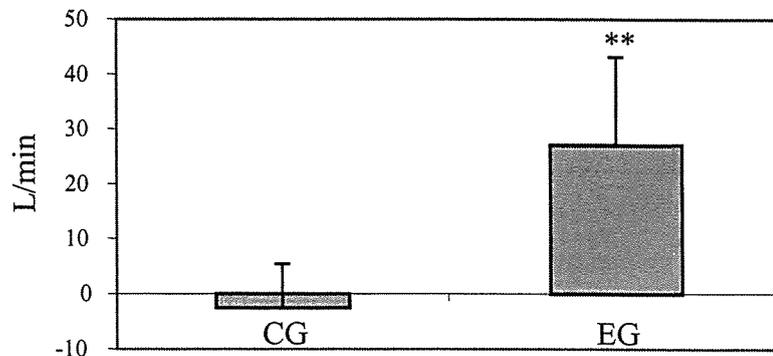
Phase III	CG n = 5		EG n = 6		p value
	Mean	SE	Mean	SE	
Peak VE (L/min)	62.04	25.71	105.82	33.29	0.040*
Peak VO <sub>2</sub> (L/min)	1.57	0.86	2.90	1.22	0.072
Peak VO <sub>2</sub> (ml/kg/min)	21.58	7.59	32.55	13.07	0.133
Peak VO <sub>2</sub> (ml/FFM/min)	31.88	11.48	46.37	16.74	0.090
Handgrip Right (units)/FFM(kg)	0.72	0.27	0.76	0.18	0.749
Bench Press (kg)/FFM(kg)	0.29	0.17	0.55	0.33	0.096
Leg Press (kg)/FFM(kg)	0.94	0.38	1.81	0.40	0.005**

\*  $p<0.05$ , \*\*  $p<0.01$

The magnitude of change between PII and PIII was calculated for the CG and EG, for all variables assessed and is illustrated in Figures 5.4a, b and c. The magnitude of change is significantly larger for the EG when compared with the controls, for peak VE ( $p<0.01$ ), peak VO<sub>2</sub> (L/min and ml/kg/min,  $p<0.05$ ) and upper ( $p<0.05$ ) and lower body ( $p<0.01$ ) strength. A mean negative change for peak VE, handgrip strength and lower body strength, was observed for the CG between PII and PIII.

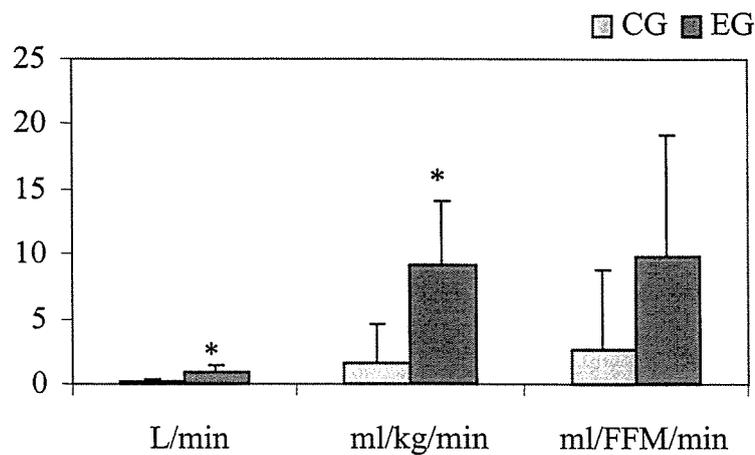
**Figure 5.4** Magnitude of change between PII & PIII for the control and exercise group (mean±SD)

(a) Peak ventilation



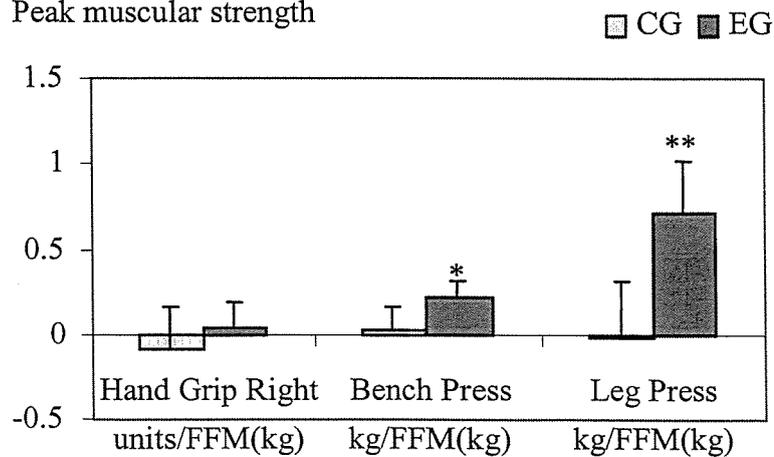
\*\* p<0.01

(b) Peak aerobic capacity



\* p<0.05

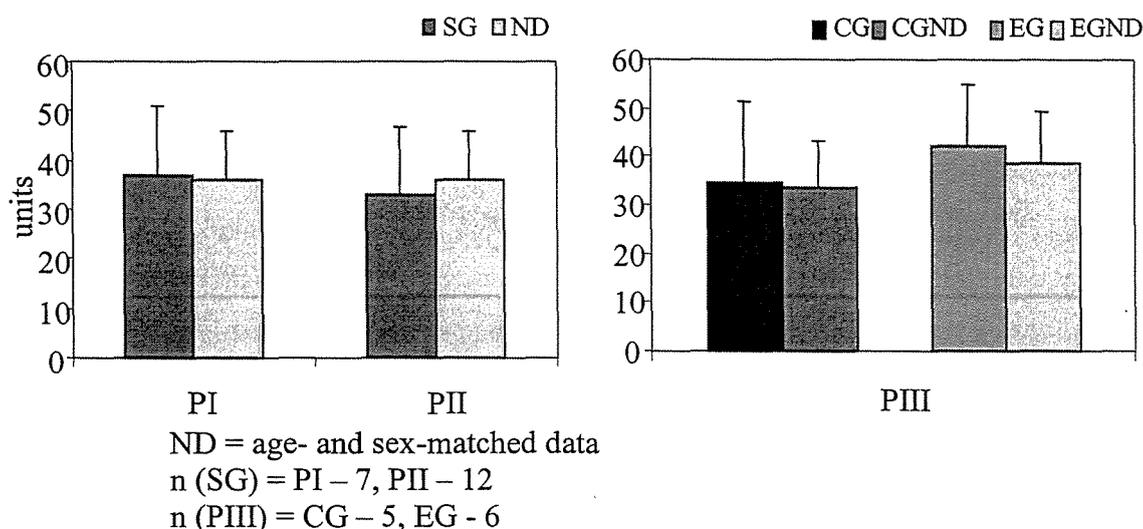
(c) Peak muscular strength



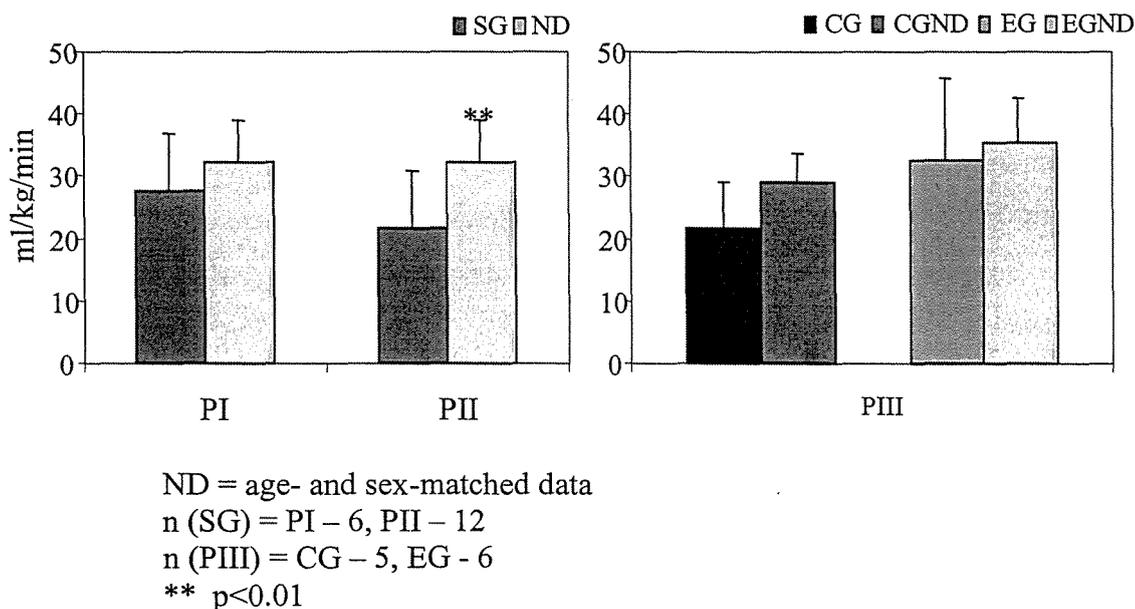
\* p<0.05, \*\* p<0.01

Handgrip strength and peak VO<sub>2</sub> data collected within the study were compared with Australian normative data<sup>144</sup> (Figures 5.5 and 5.6, respectively). These comparisons demonstrated that pre-transplant, patients experienced lower mean aerobic capacity, and similar handgrip strength, when compared with age- and sex-matched healthy controls. Undertaking a PBST was associated with declines in aerobic capacity and muscular strength, and by PII the study group was experiencing a significantly lower aerobic capacity when compared with normative data.

**Figure 5.5** Comparisons of handgrip strength (average scores between right and left) between the control and exercise group, and age- and sex-matched healthy controls (mean±SD)



**Figure 5.6** Comparisons of peak aerobic capacity (ml/kg/min) between the control and exercise group, and age- and sex-matched healthy controls (mean±SD)



## 5.4 Discussion

The results of this investigation indicated that pre-transplant, the aerobic capacity of PBST patients was below age- and sex-matched healthy controls. Additionally, undertaking a PBST was associated with further aerobic capacity decline. While the change between PI and PII scores was not significant, the magnitude of change was such that patients recorded significantly lower aerobic capacity scores when compared with age- and sex-matched data immediately post-transplant. Undertaking a PBST was also associated with detrimental changes in muscular strength, as was evident by the significant change in upper body strength between pre- and post-transplant. Participation in a regular exercise program for 3-months post-transplant has the potential to significantly improve peak ventilation, aerobic capacity and upper- and lower-body strength. Exercising patients demonstrated improvements in peak ventilation, aerobic capacity and lower body strength scores by PIII, to levels which were higher than that recorded at pre-transplant. Importantly, while the non-exercising patients also showed mean improvements in certain variables following the intervention period, the magnitude of change between post-transplant and 3-months post-transplant was significantly less for peak ventilation, aerobic capacity and upper and lower body strength, when compared with exercising patients.

### 5.4.1 Testing procedures and expression of results

Prior to the results being discussed in more detail, it is important to clarify the testing procedures implemented and the manner in which results were expressed. A maximal GXT is regarded as a valid method of assessing aerobic capacity. However, when designing the project, concerns were raised regarding the appropriateness of the testing procedure for this clinical population. Previous cancer studies have implemented methods including the 12-minute walk test<sup>247, 342, 344</sup>, and symptom limited maximal exercise tests<sup>101, 102, 104, 428</sup> to calculate aerobic fitness, and no contraindications have been reported. In support of these previous findings, no contraindications were associated with the use of a VO<sub>2</sub> max GXT for the assessment of peak aerobic capacity in this investigation. Continual ECG analysis performed throughout the entire duration of the exercise test demonstrated that there were no abnormalities present that would prevent exercise participation. In addition, the

patients were able to tolerate the maximal test, without experiencing extended periods of fatigue.

Concern with respect to undue fatigue, was also raised with regards to the strength tests implemented. However, the study patients were able to perform the 15RM upper and lower body strength tests without any extended periods of muscular soreness or injury.

The attainment of peak HR and RER greater than 1.1, during a maximal GXT are potential indicators of the ability to achieve peak  $\text{VO}_2$ . As in earlier studies<sup>102</sup>, no differences were detected in this investigation between peak HR attained during the maximal GXT throughout the testing phases. That is, regardless of the level of aerobic fitness measured, peak HR did not significantly alter throughout the testing sessions. In addition, the mean difference observed between peak HR achieved by the control and exercise group is reflective of the mean age difference between the 2 groups. Peak RER attained also showed no change throughout the testing phases. Furthermore, mean peak RER was recorded at 1.1 or greater, with the exception of mean peak RER for the CG at PI (1.05). In summary, the attainment of peak HR (which was within 10% of the age-predicted maximum), RER of 1.1 or greater, and the same peak HR and RER achieved throughout all testing phases, were indicators of the achievement of peak  $\text{VO}_2$ .

Finally, it is also important to comment on the expression of results. The relationship between  $\text{VO}_2$  and BW is well recognised and therefore peak  $\text{VO}_2$  results are commonly expressed throughout the literature in ml/kg/min. This is particularly important in a study such as this, when weight status changes. However, oxygen is transported within and utilised by lean tissue and thus when dealing with a population of changing FFM as well as BW, it is also important to adjust for FFM changes. To allow for comparisons with data in the literature, peak  $\text{VO}_2$  was expressed in two ways: the absolute value (L/min), and by adjusting for BW (ml/kg/min). To appropriately adjust for changes in body composition, aerobic fitness was also expressed in ml/FFM/min. Irrespective of the manner in which the results were expressed, a similar trend for change across time was identified.

Strength is yet another variable that is influenced by both BW and FFM. Strength values recorded in this investigation were adjusted for FFM and thus expressed as a ratio of strength values (units or kg) and FFM (kg).

#### **5.4.2 Pre-transplant function**

Comparisons with Australian normative values<sup>144</sup> indicated that PBST patients experienced a lower mean peak VO<sub>2</sub> (ml/kg/min), pre-transplant. While this mean difference was not significant, examining the aerobic capacity data on an individual basis, provided further support for the notion. Of the 6 subjects assessed at PI, 4 recorded aerobic capacity levels that placed them below the 25<sup>th</sup> percentile for normative data. The remaining 2 patients recorded fitness scores above the 50<sup>th</sup> percentile. In contrast, individual handgrip strength values were between the 50<sup>th</sup> and 75<sup>th</sup> percentile for the majority of patients assessed at PI.

As a consequence of the limited knowledge regarding pre-transplant aerobic capacity and muscular strength values, it is difficult to determine whether the poor physical condition reported in patients following a PBST is a function of the transplant or previous conventional treatment regimens often undertaken by these patients. The results of this study indicate that factors such as prior treatment, and/or cancer and treatment-related side effects such as physical inactivity may lead to a deterioration in aerobic capacity in patients who are about to undergo a PBST. These data also highlight the need for intervention programs following transplant to attain higher than pre-transplant function, rather than just a return to pre-transplant levels.

#### **5.4.3 Post-transplant function**

Undertaking a PBST was associated with declines in aerobic capacity and strength. Although the differences between pre- and post-transplant data were not significant for aerobic capacity, patients recorded significantly lower peak VO<sub>2</sub> (ml/kg/min) results following the transplant, when compared with age- and sex-matched controls. Furthermore, 42% (5 patients) of the study group assessed at PII recorded fitness values below the 25<sup>th</sup> percentile and 50% (6 patients) recorded values below the 5<sup>th</sup> percentile for normative data. The patient experiencing the highest fitness at all

testing phases, dropped from above the 75<sup>th</sup> percentile to below the 50<sup>th</sup> percentile for normative data, following the PBST. Previous research has led the American College of Sports Medicine to conclude that the initial exercise capacity of the cancer patient is in the range of 3-6 metabolic equivalents (METS) or 10.5-20.5 ml/kg/min<sup>3</sup>. The peak VO<sub>2</sub> results provided by the PII analysis (21.76±9.02 ml/kg/min) were supportive of this range.

Research reported by the ACSM (1990)<sup>4</sup> showed that significant losses in cardiorespiratory fitness occur following only 2 weeks of detraining and that a 50% reduction in aerobic capacity can occur after only 4-12 weeks of detraining. Following the treatment period, patients in this investigation, experienced 25%, 22% and 23% losses in aerobic capacity, when fitness was expressed as L/min, ml/kg/min and ml/FFM/min, respectively.

All strength measures were reduced following the transplant, with significant changes being identified for upper body strength only. During the 2–4 weeks between pre- and post-treatment tests, the study group lost 4%, 28% and 19% in handgrip, upper body and lower body strength, respectively. These rates of strength loss are in agreement with earlier research which demonstrated that strength losses can occur at a rate of 3% per day<sup>160</sup> within the first week of bed rest, followed by losses of 1-1½% per day<sup>245</sup>. The changes observed in strength measures in this investigation indicated that greater strength losses occur in muscles associated with the thigh and trunk, when compared with muscles of the hand. Between PI and PII, patients spent the majority of time in bed and were performing few movements that required upper and/or lower body strength. In contrast, any movement performed while in bed, such as eating, reading, and writing, would have predominantly required hand strength. It is possible that these arm and hand activities were able to minimise the strength losses observed for handgrip strength.

One of the most common and pervasive physiological consequences of cancer and treatment is fatigue<sup>343</sup> and a substantial contributor to cancer fatigue is low physical performance<sup>430</sup>. Following PII, it became evident that the patients in this investigation would require at least 50% of their peak aerobic capacity to undertake normal daily tasks, which often have calculated MET values of 2.5-4.5<sup>7</sup>. Moreover,

the decline observed by PII in handgrip, upper and lower body strength, highlights that both isometric and isodynamic strength is detrimentally affected and thus the ability to produce force for daily movements and tasks is adversely influenced. Loss of aerobic capacity and strength following a transplant may contribute to the presence of fatigue in this cancer population.

Due to the relatively small subject numbers within this investigation, it is possible that large fluctuations in one individual could significantly influence the mean change. However, when individual changes in aerobic capacity and muscular strength (lower body strength) were assessed, all patients demonstrated a similar trend of change and magnitude of change, with the exception of one patient. One patient assessed between PI and PII demonstrated greater declines in aerobic capacity and muscular strength, when compared with the magnitude of change experienced by the remaining subjects. The subject was female, aged 56 years and was diagnosed with multiple myeloma. She underwent a one-transplant procedure and experienced a 4.5kg and 1kg decline in weight and FFM, respectively, between PI and PII. It is difficult to explain the level of change observed as a function of these characteristics, since they were also present in other patients and were representative of the larger group. In addition, other patients assessed were either older, or experienced greater weight and FFM losses during the same period, yet did not experience the same decline in aerobic capacity and strength. The primary difference between this subject and the remaining subjects was the initial weight and body mass index. The subject who demonstrated the greatest losses in aerobic capacity and strength reported the lowest BW (44kg) and body mass index (16.9) pre-transplant. Consequently, this subject also demonstrated the lowest peak  $\text{VO}_2$  and muscular strength when expressed in L/min and absolute weight lifted, respectively, at PI. However, when BW and FFM were taken into account, peak aerobic capacity and muscular strength were close to the mean of the group

#### **5.4.4 The importance of a physical intervention program**

The differences observed between the exercising and non-exercising PBST patients, at 3-months post-treatment, highlight the importance and need to implement a physical intervention program during the recovery period. The exercising patients

recorded significant improvements in peak ventilation, peak aerobic capacity and muscular strength by 3-months post-transplant. In comparison, results for the same measures did not change between PII and PIII for the non-exercising patients.

Following the 3-month intervention period the exercising patients recorded significantly higher peak ventilation results in comparison with the control subjects. Furthermore, the exercising subjects had significantly higher peak ventilation results at PIII, when compared with immediately post-transplant and pre-transplant values. In contrast, the control participants displayed no significant change during the three testing phases. The significant difference detected between the magnitude of change experienced during PII and PIII by the control and exercising group further highlights the importance of an exercise program following treatment. While the exercising group demonstrated a mean peak ventilation improvement between PII and PIII, the control group experienced a mean decline. The results therefore indicate that participation in a regular aerobic and resistance training program has the potential to prevent further declines in peak ventilation following treatment.

The change detected in aerobic fitness for the control and exercising patients during the intervention period was similar, regardless of how the results were expressed. When assessing peak  $\text{VO}_2$  in absolute terms (L/min) or when accounting for BW changes across the phases (ml/kg/min), the control group demonstrated mean improvements, although the changes were not significant. Additionally, following the intervention period, the mean peak aerobic capacity recorded for the control participants remained less than that recorded prior to the transplant. In contrast, patients in the exercising group displayed significant changes following the 3-month intervention period, with peak aerobic capacity levels that were significantly higher than post-transplant and pre-transplant measures. Between PII and PIII, the exercising group demonstrated a significantly higher magnitude of change, when compared with the non-exercising patients. Similar trends were observed when aerobic capacity results were adjusted for changes in FFM. Participation in an exercise program induced positive changes in peak  $\text{VO}_2$ , which enabled the exercising PBST subjects to achieve higher than pre-transplant values by PIII and significantly higher values when compared with PII. In comparison, no significant

change was detected for the control group across the testing phases when aerobic capacity was measured in ml/FFM/kg.

As previously indicated, major fluctuations by one subject could significantly influence the group mean, and in turn, potentially exaggerate the results. However, upon an analysis of individual changes between PII and PIII, all exercise group subjects demonstrated an increase in peak aerobic capacity (ml/kg/min). Somewhat surprisingly and in contrast with observations of healthy subjects, those with the lowest baseline fitness, did not necessarily experience the greatest gains. In addition, those with the highest initial fitness level also did not necessarily experience the smallest gains. While there were minor changes in peak aerobic capacity experienced by all control group subjects, 4 out of 5 subjects demonstrated an increase by approximately 2-4 ml/kg/min, while one subject demonstrated a loss of approximately 4 ml/kg/min. This decline observed in peak aerobic capacity (ml/kg/min) was due to a decrease in aerobic capacity (L/min) in conjunction with a gain in BW.

The intervention program required the exercise group to perform at least 2 sessions per week of walking on the treadmill for up to 20 minutes. It is possible that the higher familiarisation with treadmill walking experienced by the exercise group in comparison with the control group, contributed to the improvements observed in peak aerobic capacity for the former group. However, as previously noted, peak HR and RER achieved during each of the graded exercise treadmill tests did not change across the testing phases, indicating that all patients in both groups attained peak  $\text{VO}_2$  at each testing session. In addition, the mean peak HR for both the control and exercise group at each testing phase was within 10% of the age-predicted maximum. Mean peak RER was 1.1 or greater, with the exception of the mean peak RER for the CG at PI.

Patients with breast cancer have shown a 20.7% increase in  $\text{VO}_2$  (1.37-1.73 L/min) following participation in a 10-week aerobic-only exercise intervention<sup>226</sup>. In comparison, the control breast cancer participants demonstrated a 1.8% decline during the same period. In this investigation, the exercising PBST patients demonstrated a higher aerobic capacity (L/min) increase of 44%, while the control

group reported a mean increase of 8%. Differences in the outcomes of these studies may reflect factors such as the type of cancer, treatment regimen undertaken, initial fitness levels of the participants, the length of the intervention period implemented, and the type of the intervention program.

When aerobic capacity results were analysed in ml/kg/min, the exercising PBST patients showed a significant increase of 39% between PII and PIII. No significant change was detected across the same period for the control participants. These results are supportive of previous findings. Following participation in a WAIT protocol, breast cancer patients demonstrated a 40% improvement, when compared with no significant change in the control groups<sup>427</sup>. Higher gains in maximal METs (4.7–7.4) of 57%<sup>101</sup> have been previously demonstrated in BMT patients following a 6-week walking program. However, in a more recent investigation performed on BMT patients categorised with excessive fatigue, only 12% gains in maximal METs (4.9–5.5) were identified following the same intervention program<sup>103</sup>.

What is of primary importance is whether the improvements demonstrated by the exercising patients in this investigation are of sufficient magnitude to allow for participation in normal daily activities without undue fatigue. A maximal MET value of 5 ( $\approx 17.5$  ml/kg/min) is regarded as sufficient to adequately perform daily tasks<sup>101</sup>. While all exercising PBST participants exceeded this level (range = 21–51 ml/kg/min), 40% of the control group failed to reach the minimum requirement (range = 11.8–32.2 ml/kg/min). Similar findings have been previously reported in BMT patients. Following a 6-week walking program, Dimeo and colleagues (1996)<sup>101</sup> found that all exercising BMT patients achieved the minimum MET value. A later investigation implementing the same 6-week walking program<sup>104</sup>, showed that 6% of the exercising patients, in comparison with 25% of the control group were unable to achieve the minimum functional requirement. Differences in the intervention duration and group characteristics may provide potential reasons for the slight variation in the results obtained between this investigation and the above 2 experiments.

Since the GXT employed per subject at each of the three testing phases was adapted to ensure the patient reached peak  $\text{VO}_2$  within a set period, exact comparisons of

peak workloads, time to exhaustion and HR at given submaximal workloads were not possible. However, the ability of all exercising patients to progress across the 3-months, in terms of aerobic exercise duration and intensity, and the ability to lift more weights and increase the number of exercises performed during the training session, is indicative of improvements within these areas. That is, for aerobic exercise, when HR at certain submaximal workloads began to decrease, workload was correspondingly increased to ensure that the patients maintained the desired exercise intensity. When patients could perform greater than 20 repetitions of a particular exercise without reaching failure, weight lifted was increased. The ability to work at a given submaximal workload with a lower HR is indicative of gains in stroke volume. In addition, since peak HR attained during each GXT test did not differ across the phases, gains observed in peak aerobic capacity were also indicative of improvements in stroke volume. The improvements observed for submaximal HR, maximal exercise duration, and peak workloads, have also been observed in exercising breast cancer patients<sup>226, 227</sup>.

Differences were detected for strength changes across the phases, between the exercising and control PBST patients. Handgrip strength values did not significantly alter across phases for either the control or exercising patients. However, while the control group demonstrated a mean loss between PII and PIII, the exercising participants showed a mean strength gain. Across the intervention period, the control group failed to show any significant change in upper- and lower-body strength, but again the mean change for lower-body strength was in the negative direction. In comparison, the exercising patients significantly improved upper- and lower-body strength across the same period. Lower-body strength of the exercising group was significantly higher at the end of the intervention period, when compared with pre-transplant levels and lower-body strength results recorded by the control group at PIII. The positive impact of the exercise program on strength is further highlighted by the results that demonstrate a significantly greater magnitude of change for upper- and lower-body strength, between PII and PIII strength scores for the exercising patients, in comparison to the control patients. In addition, the subject who experienced the least muscular strength (lower body) at PII, demonstrated the highest strength gains, while the subject who reported the highest muscular strength, showed the smallest strength gains, following the intervention period. While these changes

indicated that initial strength levels could potentially influence the magnitude of gains achieved, this trend was not consistent throughout the exercise group. That is, when the exercising patients were ranked according to their initial lower body strength and the strength gains made following the intervention program, the subject with the 2<sup>nd</sup> lowest initial strength, also experienced the 2<sup>nd</sup> lowest magnitude of gains.

As previously noted, daily tasks commonly involve isometric and isodynamic strength. Continued strength losses or alternatively, an inability to regain lost strength following the transplant will impact on the patient's ability to perform daily tasks. Furthermore, the negative magnitude of change experienced in handgrip and lower-body strength observed in the control group emphasises the risk of continued strength losses with failure to participate in physical activity following treatment cessation. Improvements in strength lead to greater muscular efficiency and a reduced effort in performing any given task. Consequently, it could be suggested that the exercise group would have a greater ability to perform normal daily activities without fatigue, when compared with the control group.

The exercising group achieved average gains of 6%, 51%, and 65% in handgrip, upper-body, and lower-body strength between PII & PIII, respectively. In comparison the control group demonstrated a 3% mean improvement in upper-body strength, in conjunction with mean strength losses of 9% and 5% for handgrip and lower body strength, respectively. The range of gains observed by the exercising group (6–65%) are slightly higher than those previously reported for adult and cardiac populations (20–50% and 20–40%, respectively), but within the range for strength improvements reported in older populations (9–227%)<sup>404</sup>.

Strength results presented within this investigation support the findings derived from studies integrating strength training within a HIV-1 population. Following a 6-week progressive resistance training program, muscular strength for the regions of the legs, chest, shoulder and arms, significantly improved pre- to post-program for those in the exercise group<sup>370</sup>. The exercising patients also experienced significantly higher levels of muscular strength when compared with the control group. These results are

comparable to the significantly higher lower body strength levels experienced by the exercising PBST group at PIII, when compared with the control group.

The inability to regain strength losses without the integration of any structured intervention has previously been shown in 36 long-term ALL survivors<sup>440</sup>. Reduced muscle strength and weakness were identified when the strength results derived from the children under investigation were matched with results from school peers. In turn, this reduced strength had a detrimental impact on the children's ability to perform basic motor skills and their level of gross motor proficiency and performance.

#### **5.4.5 Longer-term implications of PBST or BMT**

It has previously been reported that 40% of patients undertaking a BMT require a full year to regain pre-treatment fitness levels, while approximately 30% of patients are unable to return to work during the first 2 years following the transplant<sup>105</sup>. An investigation performed on 56 long-term survivors (1.5-16 years) of acute leukaemia demonstrated that 25% of patients had failed to attain 'normal' maximal aerobic capacity<sup>38</sup>. Of particular concern is that the rates of achieving normal peak VO<sub>2</sub> were the same regardless of whether less than, or more than, 8 years had elapsed since treatment cessation. A more recent investigation, which assessed the cardiopulmonary function and recovery rates of BMT patients at pre-transplant and then again at approximately 6 years post-transplant, concluded that cardiovascular impairment as a result of a transplant is persistent, but not progressive<sup>166</sup>. It seems evident from the above investigations that patients undergoing a BMT are at risk of persistent declines in aerobic capacity and strength as a consequence of a transplant. However, the results of this investigation demonstrate that adverse changes associated with a transplant are potentially reversible. Those patients who participated in a regular exercise program were able to attain higher aerobic capacity and strength levels than those recorded pre-transplant, within a 3-month period. These results demonstrate that the inability to regain pre-treatment fitness and strength is potentially the inevitable consequence of lack of aerobic and/or strength exercises, rather than adverse treatment effects.

## **5.5 Conclusion**

Undertaking a PBST leads to decrements in aerobic capacity and muscular strength, which are clinically relevant. However, while the results of earlier work indicates that 40% of BMT patients require 12 months to regain pre-treatment fitness levels, the results from this investigation demonstrate that it can take as little as three months. Moreover, this investigation demonstrates that through participation in an aerobic and strength training program, PBST patients can return to higher than pre-treatment levels, and comparable to age- and sex-matched strength and fitness levels. Furthermore, failure to participate in an exercise program following treatment may exacerbate any physical functioning losses induced by the treatment process.

# CHAPTER SIX

## STUDY THREE

### **Changes in immunological status and function following a PBST and participation in an exercise program**

*“The dogmas entrenched from the 1950s and ‘60s, of never do this  
and never do that, are pretty life threatening”  
Dr Urve Kuusk, in Kent (1996)<sup>194</sup>*

**List of abbreviations specific to Chapter six**

BMT	Bone marrow transplant
CD3+	T lymphocyte cells
CD4+	T lymphocyte helper cells
CD8+	T lymphocyte suppressor cells
DMSO	Dimethylsulfoxide
FCS	Fetal calf serum
FITC	Fluorescein isothiocyanate
I1	Intervention 1 (testing phase scheduled at 1-month post-PII)
I2	Intervention 2 (testing phase scheduled at 2-months post-PII)
I3	Intervention 3 (testing phase scheduled at 3-months post-PII)
I4	Intervention 4 (testing phase scheduled at 4-months post-PII)
I5	Intervention 5 (testing phase scheduled at 5-months post-PII)
IFN	Interferon
IL	Interleukin
MHC	Major histocompatibility complex
MTT	3-(4, 5 dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide
NKC	Natural killer cells
PBS	Phosphate buffered saline
PBST	Peripheral blood stem cell transplant
PE	Phycoerythrin
PerCP	Peridin chlorophyll-a protein
PHA	Phytohaemagglutinin
PI	Phase I
PII	Phase II
PIII	Phase III
PWM	Pokeweed mitogen
RPMI	Roswell Park Memorial Institute
SG	Study group
TNF	Tumour necrosis factor
URTI	Upper respiratory tract infections
VO <sub>2</sub> max	Maximal aerobic capacity
WBC	White blood cells

## 6. Changes in immunological status and function following a PBST and participation in an exercise program

---

### 6.0 Introduction

Cytotoxicity, prolonged bleeding, suppression of immune function, susceptibility to secondary infection and general fatigue constitute some of the side effects associated with oncology treatment<sup>429</sup>. Patients who have undergone extensive cancer treatment such as a PBST, are placed in an immunocompromised state for some time post-transplant, with T cells taking the longest period to recover to baseline levels when compared with other immune cells. Since T cells are the primary immune cells in resisting the presence of illness, the risk for the development of infections and colds is elevated during this 'open window' period. Furthermore, the presence of such conditions maintains the potential to influence the functional capacity and quality of life of PBST patients.

Currently, there is growing recognition that both acute and chronic exercise can modulate immune function<sup>354</sup>, with factors such as exercise intensity, duration, and mode of exercise influencing the type of change<sup>258</sup>. The expanding body of evidence demonstrating the effects of exercise on immune status and function has raised the hope that a suitably graded exercise prescription might be a valuable adjunct to the treatment of cancer, not only by improving functional capacity, but by also counteracting immunological disturbances<sup>349</sup>. Within the limited research available in the area of exercise immunology and cancer, studies have predominantly assessed the role of exercise in enhancing tumour defense by the innate component of the immune system. Consequently, cells within the adaptive component of the immune system, such as T cells, have been given little attention.

### 6.0.1 Purpose

Objective 1: To investigate changes between pre- and post-PBST measures of T cell numbers and function.

*Research hypothesis for objective 1:*

T cell numbers and function will be adversely affected following a PBST (as determined by pre- and post-transplant measures).

Objective 2: To investigate the role of a three-month duration, moderate intensity, mixed type exercise program on T cell numbers and function, post-PBST.

*Research hypothesis for objective 2:*

Participation in the exercise program will lead to a faster recovery of T cell numbers and function, when compared with the recovery of T cell numbers and function of non-exercising PBST patients (as determined by pre- and post-intervention measures).

## 6.1 Literature Review

The human immune system has the ability to distinguish foreign substances from those of our body, become activated and subsequently neutralise and remove potential pathogens, while coordinating tissue repair and to finally return to a surveillance condition<sup>146</sup>. The immune system has been defined as consisting of both specific and nonspecific defenses against foreign materials, where the innate and adaptive or acquired components represent the specific mechanisms<sup>354, 368</sup>. The innate defense mechanism is always ready for action and contains various cellular elements including natural killer cells and numerous types of phagocytes (neutrophils, eosinophils, basophils, monocytes and macrophages), together with important soluble factors: acute phase proteins, complement, lysozymes, and interferons. The ability to acquire a response to specific antigens arises from the adaptive system. This component of the immune system consists of specific cells, T and B lymphocytes and soluble factors, immunoglobulins. In order to understand the potential role exercise may play on the immune system of patients with cancer, it is important to first understand the role of specific immune cells and the interrelationships between the immune and endocrine systems.

The innate immune cells that have been given much of the attention throughout the literature are monocytes, natural killer cells and neutrophils. Monocytes are immature macrophages that are produced in the bone marrow, and released into circulation in response to several cytokines, where they function as phagocytic cells, cytokine producers, presenter of antigens and as blood-clotting regulators<sup>436</sup>. Once monocytes reach their destination to fixed sites along specialised vessels, they mature into macrophages.

The activated macrophage plays a dominant role in first-line immune defense against tumour cells<sup>436, 438</sup>, as an initial phagocytic agent, an antigen-presenting cell, and an initial source of interleukin-1 (IL-1), interferon (IFN) and various stimulating factors<sup>165</sup>. Their function requires several capacities including adherence, chemotaxis, phagocytosis, and a respiratory burst and release of toxic products, which ultimately leads to death of the ingested organism. In addition, macrophages maintain a role in coordinating tissue repair in an injured muscle. Interleukin-1, IFN-

gamma, tumour necrosis factor-alpha (TNF-alpha), and macrophage-activating factor regulate the antitumour activities of the macrophages.

Lymphocytes that lack identifying surface markers comprise null cells, with one particularly important subgroup of null cells being the natural killer cells (NKC)<sup>47</sup>. Natural killer cells account for 10–15% of all circulating mononuclear cells. The cells provide an important nonspecific first line of defense against many types of tumour cells with the rate of metastasis being inversely proportional to the level of NKC function. Furthermore, NKC demolish some virus-infected cells and act in the repair process of injured muscle<sup>289, 355</sup>. Natural killer cells maintain the capacity to function without needing to recognise cell-surface associated major histocompatibility complex (MHC) molecules<sup>277</sup> and can influence the behaviour of target cells including tumours, by the production of cytokines<sup>165</sup>.

Neutrophils are one of the body's most efficient phagocytes of many microbial, bacterial and viral pathogens, act as a first line of defense against infectious agents, and constitute about 60% of circulating leucocytes<sup>259, 308, 439</sup>. Additionally, neutrophils are involved in the synthesis and release of immunomodulatory cytokines that influence T and B cell activities<sup>308</sup>. Tumour cells can be destroyed by neutrophils through their production of peroxides and free radicals<sup>265</sup>.

The 2 specific adaptive immune cells important to note are the T and B cells. T cells (CD3+) are lymphocytes that are coded in the thymus in response to both specific allergens and nonspecific mitogens<sup>44</sup>. They comprise cells that have a distinguishing antigen – helper cells (CD4+) and suppressor (CD8+) cells. Foreign antigens, in the context of Class II MHC molecules, expressed on the surface of antigen-presenting cells are recognised by helper T cells<sup>355</sup>. For example, macrophages release IL-1, which is a signal for the activation of T helper cells. In turn, IL-2 is produced by the activated T cells and can synergise with interferons to further elevate T cell activity. Additionally, IL-2 has the ability to stimulate the secretion of another lymphokine (IL-3) by the helper T cell. The dispatch of a signal to cytotoxic or suppressor T cells is initiated potentially by this latter substance. The cytotoxic T cells act by destroying abnormal cells that are recognised by foreign surface constituents. B cells are activated by the helper T cells, proliferate and differentiate into plasma cells, with

a resultant antibody release, while the helper T cell action is controlled by the suppressor T cell via a negative feedback mechanism. It has been noted that the ratio of helper to suppressor cells is a critical variable, where susceptibility to infections may be elevated if the ratio falls below 1.5<sup>191</sup>.

### 6.1.1 Immune system status

The status of the immune system is associated with the endocrine system. The endocrine system has a distinct role of signalling a network of hormones and neurotransmitters that act to regulate cell function throughout the body<sup>276</sup>. Catecholamines are known to exert a significant effect on various cellular components of the immune system, including mediation of leucocytosis, functional changes in leucocyte subsets and modulation of NKC number and activity<sup>308</sup>. Catecholamines facilitate leucocytosis by reducing adhesion of leucocytes to the endothelial cells that line vessel walls<sup>416</sup>. Furthermore, CD3+, CD4+ and CD8+ lymphocytes are functionally enhanced by catecholamines through alpha-adrenergic stimulation. However, beta-adrenergic impulses inhibit CD4+ and CD8+ proliferation through catecholamine blood levels, and also by the number of beta-adrenoceptors on lymphocytes<sup>416</sup>.

Other hormones known to influence the immune system are cortisol, growth hormone and insulin. Cortisol is considered to be a 'broad-spectrum' immunosuppressive agent that affects the activity of several types of immune cells and may reduce circulating lymphocytes by the action of re-trafficking them to peripheral tissues<sup>256</sup>. Growth hormone (a neuropeptide) is essential for the development and maintenance of immunocompetence and the enhancement of lymphocyte proliferation, T lymphocyte and NKC cytotoxicity. Additionally, growth hormone primes the microbicidal activity of the macrophage cell<sup>308</sup>. Finally, insulin maintains a primary role in immune cell metabolism. The insulin-mediated glucose influx, for which the interaction between insulin and its receptors and the activation of glucose transporters are responsible, supports the energy demand of immune cells<sup>416</sup>. The uptake of amino acids and protein metabolism in lymphocytes is further facilitated by insulin<sup>416</sup>.

As a consequence of the relationship between the endocrine and immune system, any event of a psychological or physical nature that leads to a change in certain hormone levels, maintains the ability to influence the status of the immune system. Elevated stress hormone levels, accompanied by an increase in the activation of the sympathetic nervous system or the hypothalamic pituitary adrenocortical system, have been associated with certain life stressors such as bereavement, loneliness, divorce, and unemployment. Additionally, the presence of these stressors has also been shown to yield a negative impact on the immune system<sup>204</sup>. Furthermore, affective states such as anxiety and depression have been associated with declines in NKC cytotoxicity, mitogen responsiveness, T cell ratios and T lymphocyte numbers<sup>448</sup>.

Cohen and associates (1991)<sup>71</sup> tested the link between the endocrine and immune system by assessing degrees of psychological stress via questionnaires, followed by dosing 394 healthy subjects with nasal drops containing one of five respiratory viruses. An additional 26 subjects were given saline nasal drops. The results demonstrated that the rates of both respiratory infection and clinical colds significantly increased in a dose-response manner with increases in the degree of psychological stress. Controlling for age, sex, education, allergic status, weight, the season, personality traits and other various factors did not alter these results. Research findings have also linked bereaved spouses with elevated cortisol and decreased NKC lysis<sup>173</sup>, and lonelier medical students with lower levels of NKC activity<sup>196</sup>.

Furthermore, enhancement of the immune system has been demonstrated via a behavioural stress reduction intervention<sup>197</sup>. On completion of the 4-week relaxation training program, the NKC activity of older adults significantly increased in conjunction with a decrease in distress-related symptomatology. In contrast, no significant differences were observed in these same measures for the control group or social contact only group.

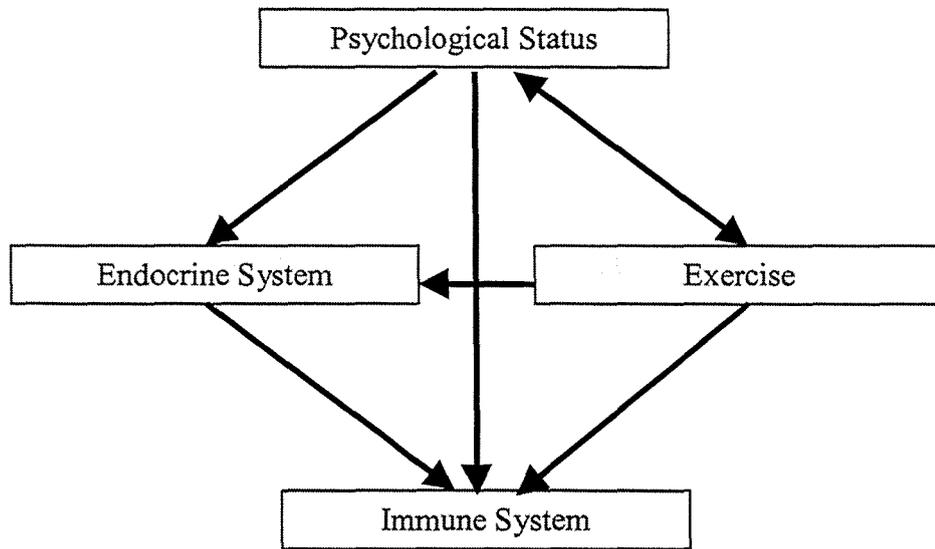
In summary, psychological stress may indirectly influence the immune system through the release of the immunomodulatory hormones. However, just as psychological stress has been related to the release of stress hormones, so too have

physical stress conditions such as exercise. Common to exercise are increases in plasma cortisol, epinephrine and norepinephrine concentrations<sup>286</sup>.

The individual endocrine response to exercise is dependent on the nature, intensity and duration of the exercise session, and the initial fitness level of the participant<sup>308</sup>. Intense exercise (more than 60% VO<sub>2</sub>max) will generally activate both the sympathoadrenal and pituitary-adrenocortical endocrine system, leading to an increase in the plasma concentration of catecholamine (epinephrine and norepinephrine) and glucocorticoid hormones (such as cortisol). The relationship of catecholamines and cortisol, and immune function has been summarised as follows. Following high-intensity exercise, a transient increase in the circulating lymphocyte count is caused by epinephrine, while the longer-acting cortisol quickly dominates events during recovery, causing marked and prolonged lymphocytopenia and neutrophilia<sup>256, 259</sup>.

Physical activity can influence a person's psychological state by inducing either a calming or stressful effect. While an appropriate dose of exercise can correct a depressed mood state, an inappropriate dose can further deteriorate a negative mood. Exercise set at an intensity that a patient finds difficult to perform, may lead to feelings of helplessness and thus further contribute to a reduced self-perception and physical well-being<sup>149</sup>. As previously discussed, distress may increase the release of glucocorticoids and thus result in an immunosuppressive effect. Conversely, the potential benefits of an appropriate exercise prescription on psychological status have also been shown. The beneficial changes observed in mood states tend to be greater in an individual who initially has high stress, anxiety or depression levels, when compared with the person who is in a positive mental state<sup>349</sup>. The association between exercise, psychological status, the endocrine system and the immune system is illustrated in Figure 6.1.

**Figure 6.1** The link between exercise, psychological status, the endocrine system and the immune system



### 6.1.2 Immune system status of patients with cancer

The immune status of patients with cancer is potentially influenced by a number of factors including the psychological status of the patient, the cancer present and treatment regimens undertaken. Depression, worry, fear, and other negative psychological states are common characteristics known to exist in patients with cancer<sup>105</sup>. The relationship between the presence of these psychological states, and the release of hormones that evoke immunomodulatory effects, has already been discussed. It has also been noted that patients with cancer who are experiencing prolonged anxiety may continually activate the hypothalamo-pituitary-adrenal axis, in conjunction with the sympatho-adrenomedullary axis. In turn, this may lead to immune suppression, an increase in susceptibility to infection and slow reconstitution of immune function following treatment, while enhancing the risk of cancer recurrence<sup>12</sup>.

In addition to the effect of psychological status on immune function, is the influence that the cancer and its associated treatment might impose. Impaired immune function has been considered a 'hallmark of malignant disorders'<sup>356</sup>. Various studies reported in Britenden et al (1996)<sup>53</sup> have shown that peripheral blood natural

cytotoxicity (NKC cytotoxic function) is significantly reduced in patients with familial and nonfamilial melanoma, head and neck, lung, ovarian, cervical, bladder, prostatic, hepatocellular, pancreatic, oesophageal, breast and various combined cancers, when compared to non-cancerous controls. However, others have documented that the natural cytotoxicity does not change in patients with colorectal, pharyngeal and breast cancer, irrespective of the stage of disease. Brittenden et al (1996)<sup>53</sup> further noted that a wide biological variation exists in the NKC number and activity of healthy controls. Therefore, interpreting studies on natural cytotoxicity in patients with cancer is difficult. Overall, however, a trend for reduced NKC activity in certain cancers is emerging.

T lymphocyte subsets and lymphocyte reactivity in the peripheral blood from patients with various types of urological cancer, compared with age-matched controls have also been studied<sup>190</sup>. A depression in immune competence was found in the group of male patients with infiltrating bladder cancer. In more than 50% of these patients, CD4+ cell numbers were reduced with a corresponding inversion of the CD4+/CD8+ ratio and an impairment of T cell function. In contrast, the patients with superficial bladder carcinoma and those with renal cell carcinoma demonstrated a similar immune profile to that of the control group. Lastly, the group diagnosed with prostatic carcinoma had reduced CD8+ cells and thus reported higher mean CD4+/CD8+ ratios when compared with controls.

The relationship between stage of disease and cytotoxicity has not been well defined<sup>53</sup>. While some investigations have reported a reduction in cytotoxicity with disease progression<sup>84, 360, 391</sup>, others have not found the same correlation<sup>244, 374</sup>. With regard to the T lymphocyte response, a poorer proliferative response of peripheral blood mononuclear cells in response to phytohaemagglutinin (PHA) in breast cancer patients has been reported, with the degree of defect being directly correlated to stage of disease, including tumour size and lymph node status<sup>423</sup>.

Anti-cancer treatments including surgery, radiotherapy and chemotherapy also have the potential to influence natural cytotoxicity<sup>53</sup>. In regards to surgery, a post-operative immunosuppression has predominantly been observed, with the onset of impaired immune function being dependent on various factors including pre-

medication and anaesthetic agents used, type of surgery performed and peri-operative blood transfusions<sup>53</sup>.

Most chemotherapeutic agents produce a cytotoxic effect in a wide variety of normal tissues<sup>53</sup>. Neutropenia is often a complication of chemotherapy, increasing the patient's risk of susceptibility to infection, colds or flus<sup>161</sup>. It is these cytopathic effects of myelosuppression, lymphopenia and bone marrow reserve depletion, that provide potential limitations for the use of many current cancer therapies to combat any residual disease<sup>51</sup>. Animal studies have shown that drugs such as cyclophosphamide, vinblastine and methotrexate inhibit NKC activity, whereas vincristine has been shown to elevate NKC activity<sup>53</sup>.

The effect of radiotherapy on NKC counts and activity may ultimately depend on the extent of the underlying disease, the dosage delivered and the area of tissue irradiated<sup>53</sup>. For example, intra-operative radiotherapy such as that used in the treatment of pancreatic cancer, utilises a small radiation field and consequently does not inhibit NKC activity<sup>443</sup>. In contrast, radiation to areas such as the chest or pelvic region has been shown to influence blood lymphocyte populations and NKC activity. Patients with breast cancer have demonstrated a significantly reduced NKC activity<sup>43</sup>, while patients with lung cancer have shown a reduction in the number of circulating lymphocytes, following radiotherapy<sup>393</sup>.

Of specific relevance to this investigation is the impact of a PBST on immune function. As a consequence of the high-dose treatment received as part of a PBST, immune function is significantly impaired following transplantation and infectious complications are common<sup>249</sup>.

An imbalance in the CD4+/CD8+ ratio, impairment in T cell function, a reduction in IL-2 production and/or a failure to respond to endogenous IL-2, have been demonstrated following PBST and BMT<sup>384</sup>. Additionally, diminished B cell function, cytokine production and/or levels of soluble cytokine and T cell receptor levels in the serum have been noted. The speed at which the immune system recovers following a transplant is in part determined by whether a PBST or BMT has been undertaken. In general, the recovery of the immune system tends to be faster in

patients who have undergone a PBST<sup>216</sup>. Monocyte and NKC counts have usually recovered within the first month post-transplantation, while recovery of T cell counts generally occurs within 6 months post-transplant. Although T cell counts may take up to 6 months to fully recover, the CD4+/CD8+ ratio tends to be markedly decreased for a longer period post-transplant<sup>384</sup>. Others have also reported that T cell subsets display an increase in CD8+ frequency within the first 3-months post-transplant in conjunction with a decrease in CD4+ cells and the CD4+/CD8+ ratio (mean ratio of  $0.3 \pm 0.2$ )<sup>158</sup>. Furthermore, the ratio failed to return to normal with 4-6 months post-transplant. T cell function has also been shown to adversely change following transplantation. It was suggested that high levels of suppressor cell activity following the transplant may provide, in part, the origin of the decreased total T cell function<sup>384</sup>.

In summary, immune cell recovery following a transplant usually occurs in the order of neutrophils, monocytes and NKC first, followed by CD8+ cells, B cells and then lastly CD4+ cells<sup>384</sup>. It thus seems plausible that patients may experience an “open window” period to infections and colds, up to a period of 6 months following a PBST. Therefore, methods that have the ability to initiate faster immune cell recovery post-treatment could potentially influence the patient’s presence of illness post-transplant and thus their state of health and quality of life.

Evidence demonstrates that participation in exercise can influence the state of the immune system. It is the relationship between the immune system and physical activity that has attracted the attention of clinicians concerned with either the prevention or treatment of cancer, autoimmune diseases, HIV infections and transplant rejections<sup>355</sup>.

### **6.1.3 Exercise and the immune system**

In order to understand the role exercise might play in influencing either cancer prevention or recovery of the immune system following cancer and treatment, it is crucial to first understand the immune defenses against tumour cells. Once a tumour has been developed, the basic processes of immunoprotection include a slowing of its growth rate (cytostasis) and destruction of the abnormal cell (cytolysis). Tumour

promoters include factors that suppress immune function, while factors that enhance immune function could be regarded as inhibitors. The initial step in cytotoxicity is the presentation of tumour antigens to T and B cells via antigen-presenting cells, macrophages and monocytes. Secretions of various cytokines through the resulting activation of the CD4+ (T helper) cells stimulate the cytotoxic activity of T cells, NK cells, macrophages and neutrophils. The process of cytotoxicity involves an adhesion between the immune cell and the tumour target, the insertion of pores into the membrane of the tumour cell and the injection of cell-specific molecules through these pores, which ultimately rupture the tumour cell membrane. Antibodies produced by the B cells aim to counter the tumour antigens, and certain cytokines including both IFN and TNF may exert a cytotoxic or cytostatic effect in their own right<sup>31</sup>. It is therefore important to determine what type of physical activity leads to an enhancement of the immune system, and could thus potentially influence cancer development or progression. Moreover, an evaluation of the literature examining the exercise response of specific immune cells is required.

Several investigators<sup>240, 266</sup> have reported an increase in peripheral venous leucocyte count roughly proportional to the intensity and duration of the exercise bout. However, leucocyte counts may reduce prior to the termination of exercise if the activity bout is of a prolonged duration<sup>127</sup>. Taking these two factors into consideration, it seems plausible that leucocyte counts may increase with increasing duration up to a certain time point, however they may reduce prior to the end of the exercise bout, once the particular time point has been reached. Determining exactly when this time point occurs requires further research.

The acute response of macrophages to exercise has been examined extensively by experimental studies. The macrophage and monocyte counts in peripheral blood are increased transiently by a given exercise bout (irrespective of duration or intensity). However, normal values are obtained within minutes, or at most, hours of recovery<sup>436</sup>. Counts are often unaffected by training, but seven days of exhausting training has been found to decrease the macrophage response. Woods et al (1999)<sup>439</sup> reported extensive evidence linking acute and moderate, and acute and exhaustive exercise with enhanced macrophage activity by increasing their enzyme content, phagocytic and cytotoxic activity, chemotaxis and adherence. Other researchers

maintain that while macrophage function is enhanced with moderate exercise, it is impaired with heavy exercise.

Of all the lymphocyte subsets, the most responsive to exercise stress are NKC<sup>439</sup>. An increase in NKC number and activity during exercise has been demonstrated in a number of studies, with a transient fall of number and/or activity post-exercise<sup>259, 264, 287, 289, 352, 354, 392</sup>. However, the suppression in NKC numbers was not observed following intensities of 25% and 50% VO<sub>2</sub>max<sup>392</sup>. The increase in NKC number with exercise has been attributed to an increase in NKC activation and potentially an elevation of recycled NKC<sup>223</sup>. Additionally, Shephard (1994)<sup>351, 355</sup> reported research demonstrating that a catecholamine-mediated decrease of cell margination may potentially induce the rise in NKC. The fall in NKC activity post-exercise or during prolonged exercise may be attributable to an increased prostaglandin release by the monocytes<sup>289</sup> or serum cortisol levels<sup>351, 355</sup>. However, restoration of normal resting levels of NKC function occurs within a few hours post-exercise, and there is often a partial compensation even for the immediate suppression of the NKC by a favourable change in the T-helper/T-suppressor ratio.

As a result of the catecholamine-mediated demargination of cells from endothelial tissues and bone marrow, or as part of the phagocytic and inflammatory response to exercise-induced tissue damage, the circulating number of neutrophils increases with exercise<sup>308</sup>. Neutrophils undergo adherence, phagocytosis of bacteria or tissue fragments, degranulation of cytoplasmic granules, and ultimately activation of the respiratory burst following mobilisation into the circulation and migration into tissues<sup>308</sup>. Evidence also indicates that the production of peroxides and free radicals is increased for as long as 6 hours following an acute exercise bout, thereby increasing the killing capacity per cell<sup>353</sup>. It is possible to tentatively conclude that exercise acts to recruit inactive cells into a pool that are able to respond to stimuli, and leads to a relatively small elevation in cell activity<sup>417</sup>. However, only moderate exercise is associated with a prolonged improvement in the killing capacity of these cells, while exhaustive exercise has the opposite effect<sup>259</sup>.

The impact of exercise on T cells has been demonstrated in studies assessing lymphocytes. The effect of high- versus moderate-intensity exercise on lymphocyte

changes has been investigated, with findings demonstrating that greater lymphocytosis, represented by T and NKC counts, was associated with high-intensity exercise<sup>263</sup>. Following exercise, lymphocytopenia was documented for both intensities, but was greater following high-intensity exercise when compared to moderate-intensity exercise. Others have identified changes in the T cell ratios with suppressor cells increasing from 33–36%, a reduction in helper T cells from 54–43% and a corresponding ratio drop from 1.94 to 1.36 following exercise<sup>28</sup>. Similar T cell ratio drops following a bout of maximal or exhaustive exercise have been identified in more recent investigations<sup>164, 215</sup>. However, an investigation assessing T cells following endurance running did not find any change in the T cell ratio<sup>265</sup>.

Acute exercise has also been shown to influence the release of cytokines. Exercise typically increases the production of IL-1 and resting levels are sometimes enhanced by training<sup>110, 352</sup>. The effect of acute exercise on IL-2 is commonly a depression of plasma levels<sup>317</sup>. However, the effect is not always a depression of function, since sustained moderate exercise that elevates core temperatures may expand plasma levels of IL-2, and the substantial up-regulation of IL-2 beta receptors may further enhance the IL-2 response<sup>289</sup>. Following training, rises in the NKC count may be responsible for the particularly large gains of IL-2 beta-receptor activity seen. The impact of exercise and training upon IFN levels has been relatively inadequately studied. However, an increase following a moderate exercise bout of 60 minutes duration has been reported<sup>110</sup> and elevated levels of TNF-alpha have also been detected following moderate exercise<sup>229</sup>.

In summary, participation in exercise is most likely to influence the protection against cancer through the exercise-induced rise in the number and/or activity of macrophages, NKC and their regulating cytokines<sup>353</sup>. Since most of the immediate immune responses to exercise are relatively short in duration, susceptibility to cancer is more likely to be affected by training-induced changes in resting function of the immune system than by immediate responses to an exercise bout. Simon (1987)<sup>361</sup> supported this view by commenting that since the acute exercise response is usually quite transient in nature, impact upon the normal defense against bacteria, viruses and neoplastic cells is likely to be minor. It was also noted that depending on the type, intensity and duration of exercise undertaken, the immune response to the

exercise bout may vary from day-to-day with an enhanced response on one occasion and a suppressed response on another<sup>191</sup>.

Information required for determining the immune response to continuous and regular training can be obtained by evaluating cross-sectional investigations. Granulocytosis, lymphocytosis and an increase in antibody-dependent cytotoxic and NKC activity, are the most consistently observed features in resting athletes<sup>265, 288</sup>. Investigations reported by Nieman and colleagues (1993)<sup>264</sup> have illustrated that NKC activity was enhanced in physically active Japanese men compared with their sedentary counterparts, highly conditioned elderly women versus sedentary elderly women, and in elite cyclists relative to untrained subjects.

A cross-sectional survey examined whether habitual endurance exercisers retained a higher level of T cell function when compared with sedentary age-matched controls<sup>358</sup>. Immune senescence was also assessed by comparing the sedentary and exercising elderly groups with young healthy controls. Results observed included a lower circulating CD3+ and CD8+ cell count in conjunction with a trend toward a higher CD4+/CD8+ ratio in the elderly, when compared with the young. Furthermore, higher percentages of activated CD3+ and 'memory' CD4+ and CD8+ cells were also found. While comparison between the exercising and sedentary group demonstrated no differences in circulating counts of immunocompetent cells, the active elderly subjects showed a significantly greater T cell proliferative response and related cytokine production.

In comparison, other cross-sectional investigations have reported poorer immune function in exercising subjects compared with sedentary controls. McCarthy and Dale (1988)<sup>240</sup> demonstrated that at any given absolute work-rate, the sedentary subjects experienced a higher level of leucocytosis when compared with athletes. Phagocytic activity has been shown to be poorer in athletes, and lower lymphocyte, T helper, T ratio and NKC counts were observed in athletes undergoing controlled intensity training when compared with healthy untrained men<sup>355</sup>.

Others have reported no significant differences in baseline immunocompetence as a result of regular training<sup>260, 317</sup>. Natural killer cell and T cell function of highly

trained runners and cyclists were compared with sedentary controls, and no differences were found. It was also noted that NKC activity and T cell function were unrelated to aerobic capacity. Furthermore, a comparable leucocytosis has been observed when the two groups were exercised maximally.

As a consequence of the available evidence regarding the effect of acute and chronic exercise on immune status, many researchers<sup>217, 224, 235, 254, 308, 417, 438</sup> claim that moderate exercise enhances immunity, while more strenuous exercise and prolonged training appear to suppress it. Nieman (1994)<sup>259</sup> modelled this theory by describing the relationship between exercise and upper respiratory tract infections (URTI) in the form of a 'J' curve. The model suggests that participation in moderate exercise training may reduce the risk of URTI, while participation in periods of excessive amounts of high-intensity exercise may elevate the risk. However, other investigators<sup>224, 225</sup> have not demonstrated consistent support for such a model. Attempts to compare resting immune function in athletes and non-athletes have been unable to provide crucial evidence that links clinically important immune changes with athletic endeavour<sup>267</sup>.

Investigations analysing the clinical significance of changes in immune function with exercise are scarce. Furthermore, in the few studies identified, the clinical changes identified have been in the presence of adverse, no change or improved immune system status.

An investigation performed on elite swimmers undertaking intensive training found that swimmers had significantly lower neutrophil oxidative activity at rest when compared with matched controls<sup>309</sup>. However, while oxidative activity was lower, URTI rates did not differ between the swimmers and controls. Others have shown that near-daily brisk walking, compared with inactivity, reduced the number of sickness days by half over a 12- to 15-week period<sup>262, 265</sup>. However, this change occurred without a change in resting immune function. Finally, it has been demonstrated that elderly women classified as 'aerobically sedentary' experienced the highest incidence of URTI, while the highly conditioned subjects maintained the lowest incidence<sup>262</sup>. In association with these findings, NKC and T cell function were most superior in the highly conditioned elderly women. Taken together, these

results suggest that higher NKC and T cell function is associated with a reduction in the presence of URTI.

It seems evident that while the clinical significance of the effect of exercise on the immune system remains unclear, it is widely accepted that exercise can influence the status of the immune system, with the type of change being dependent on the nature of the exercise. It is this relationship between exercise and the immune system that has led to investigations assessing the effect of exercise on patients with a compromised immune system, such as those with cancer.

#### **6.1.4 Exercise, cancer and the immune system**

The potential benefits and detriments that exercise may have on the immune system has been discussed above. The state of the immune system following neoplasia and cancer treatment has also been highlighted and is generally regarded as suppressed<sup>359</sup>. Therefore, it is of great interest to determine whether exercise can play a positive role in enhancing an already suppressed immune system in patients with cancer. Concurrently, there is concern that exercise may further deteriorate the immune system, placing the patient at an even greater risk of infection. Unfortunately, evidence describing the role of exercise in immune cell recovery post-cancer and treatment is scarce and thus neither view can as yet, be accepted.

Animal investigations have been performed to further define the relationship between cancer, the immune system and exercise. Results derived from these studies have been inconsistent due to methodological differences<sup>210, 437</sup>. Nevertheless, these investigations have generally shown that the resistance of animals to experimentally-induced tumours is enhanced through participation in an exercise program<sup>353</sup>, and that tumour growth rate is slowed when animals are trained 1-8 weeks prior to tumour induction<sup>165</sup>. Woods et al (1994)<sup>437</sup> found that moderate exercise training in rats increased the phagocytic capacity of intratumoural phagocytic cells, when compared with those of the exhaustive training or control group. However, these changes had no apparent effect on tumour incidence or progression.

Unfortunately, little data regarding changes in immune cell number and function in exercising cancer patients are available. The investigations available have predominantly assessed NKC number and activity, since this is the immune surveillance cell for the first-line defense against cancer<sup>446</sup>.

Resting NKC activity was enhanced in women with breast cancer after participating in a 7-month moderate exercise program<sup>292</sup>. Baseline NKC activity levels in patients with breast cancer were lower (18.9% lysis) when compared to healthy subjects (30-35% lysis). However, following the exercise intervention, cytotoxic activity was enhanced by 28.3%. The changes in NKC activity occurred in the absence of changes in cell number and percentage. Natural killer cell number and percentage of the breast cancer group were within normal range and were comparable with values of healthy athletes at each testing time point. A further study, again investigating breast cancer patients<sup>293</sup>, identified that following 7-months of moderate exercise training there were significant leucocyte subpopulation changes and that granulocyte concentration was significantly enhanced. In contrast to the rise observed in granulocytes, the percentage of lymphocytes and monocytes decreased. Two tests were implemented to assess monocyte function and demonstrated that monocyte phagocytotic capacity was improved against receptor-destroying, enzyme-treated sheep red blood cells following training, but was unchanged against Anti-D loaded human erythrocytes.

Immune changes of breast cancer patients who had undergone surgery, chemotherapy and/or radiotherapy, following an 8-week exercise intervention have also been assessed<sup>261</sup>. It was found that the exercise program induced no significant effect over NKC activity, and concentrations of T cell and NKC counts. However, it was also identified that those patients who had been diagnosed and treated for an average of three years, maintained NKC activity levels similar to healthy controls.

The effect of a 14-day moderated exercise program, utilising an arm and bicycle ergometer, on NKC cytotoxic activity has been studied among stomach cancer patients<sup>446</sup>. The study suggested that early moderate exercise has a beneficial effect on the function of in vitro NKC activity in patients with stomach cancer following curative surgery. This conclusion was based on findings that demonstrated a drop in

NKC activity until postoperative day 7 for both the control and exercising group, followed by an increase in the mean NKC activity of the exercise group, and a continued decrease in the control group, by day 14. At day 14, the exercise group was demonstrating significantly higher NKC activity levels when compared with that of the control group. It could be suggested that these are clinically significant findings since others have reported that disease-free treated patients with high peripheral blood NKC activity have demonstrated a significantly longer metastasis-free survival time than those with low NKC activity<sup>307</sup>.

Changes in immune parameters associated with a 12-week aerobic training intervention were assessed on 6 children aged between 13-14 years of age, successfully treated for acute lymphoblastic leukaemia and other types of neoplasms<sup>359</sup>. Three out of six of these children fully completed the 12-week program and were receiving chemotherapy during the course of the study. While all six children participated in the initial and final exercise tests, only the results from the 3 exercising children were presented and compared with the results from the control participants. The investigation found that those children who had been diagnosed with cancer were experiencing a suppressed immune system when compared with healthy matched controls, evidenced by the low leucocyte, lymphocyte, monocyte and granulocyte counts during the initial testing phase. It also appeared that participation in the exercise program led to a continued decline in certain aspects of immune effectiveness, as could be identified by the change in T cell counts and the helper/suppressor ratio. CD3+, CD4+, CD8+ and the CD4+/CD8+ ratio was reduced from 0.51±0.17, 0.31±0.12, 0.27±0.07, and 1.1±0.2, respectively, at the initial testing phase, to 0.28±0.07, 0.13±0.03, 0.20±0.19, and 0.9±0.3, respectively, during the final testing session. In addition, spontaneous, and IL-2 induced cytolytic activity, and PHA- & PWM- (pokeweed mitogen) induced proliferation were also reduced. However, it was noted that major increases in susceptibility to either infection or spontaneous neoplasia are unlikely while the CD4+ counts exceed 200 cells x 10<sup>6</sup> cells/L and the CD4+/CD8+ ratio exceeds 0.2. Therefore, it was believed that the observed changes in the immune system remained insufficient to cause concern for health. Unfortunately, since the data from the 3 children who failed to complete the exercise program were not shown, it is difficult to accept exercise as the primary cause of the continued immune system decline.

Previous research has demonstrated that chemotherapy treatment is associated with adverse immune changes and it was unclear in this investigation which subjects were still receiving chemotherapy treatment.

Finally, duration of neutropenia and thrombopenia were assessed in patients with cancer receiving high-dose chemotherapy followed by a PBST. Thirty-three patients participated in a daily aerobic exercise program during the hospitalisation period. The results demonstrated that the exercising patients experienced shorter durations of neutropenia ( $p < 0.01$ ) and thrombocytopenia ( $p < 0.06$ ) when compared with the controls<sup>102</sup>.

Exercise immunology and cancer research has predominantly assessed the innate component of the immune system, specifically NKC. However, this study has an emphasis on determining the role of exercise on the adaptive component of the immune system, and particularly T cells. More information regarding the role of exercise and T cells can be found by analysing studies that have investigated patients with HIV.

### **6.1.5 Exercise, HIV and the immune system**

Shephard and others (1991)<sup>355</sup> commented on an investigation performed with HIV+ patients that found 4 weeks of endurance exercise increased T helper cells and elevated the T helper/suppressor cell ratio, in comparison with a reduced T cell ratio in the control subjects. These findings were supported by others, who found that T-lymphocyte levels in moderately-exercising AIDS patients can return to levels comparable to patients with AIDS who are taking treatment drugs such as AZT<sup>276</sup>. However, research reported by Ullum and associates (1994)<sup>396</sup> showed that moderate exercise training of HIV-seropositive patients may either increase, or induce no change in resting CD4+ cell counts.

Others have investigated not only the exercise response of T cells counts in HIV patients, but have also examined the NKC response<sup>204</sup>. The investigators showed that exercising patients demonstrated improvements in cardiovascular fitness, maintenance of NKC numbers and unaffected distress levels, in comparison to an

increase in anxiety and depression, and a corresponding drop in NKC numbers in the non-exercising patients. Increases in T helper cell counts were also observed in the exercising patients. This is a clinically important finding since a reduction in this cell type has been related to worsening immune function and an elevated disease progression. Furthermore, additional evidence of immune normalisation was measured by an improved ability of the exercising patients to ward off latent viruses. An earlier investigation reported similar findings with no change in NKC counts in the exercising HIV groups, while the control group demonstrated non-significant declines<sup>203</sup>. However, it was also reported that cell cytotoxicity remained unchanged in both groups.

CD4+ counts ranging from 9-804 $\mu$ L and CD4+/CD8+ ratios ranging from extremely low values of 0.02 to normal limits of >1.5, have been shown in HIV subjects<sup>319</sup>. It was also found that the disease stage was not statistically related to training-induced changes of T cell counts, and that gains in aerobic fitness were achieved in the absence of changes in total leucocytes, lymphocytes, or CD4+ and CD8+ subsets.

A literature review on changes in CD4+ enumeration in HIV-1 patients following aerobic exercise training has recently been performed<sup>205</sup>. The results were summarised as follows: regardless of the disease stage, symptomatology, or level of CD4+ cells, no decline in CD4+ counts have been observed and there is a trend toward an increase in the number of CD4+ cells in all but one investigation identified, with the more significant increases being observed in patients at an earlier stage of the disease. Possible mechanisms were related to the role exercise may play in stress management and thus the ability of exercise to have a buffering on suppressive stressor effects, thereby facilitating a return to normal CD4+ counts. Collectively, the studies reviewed provided supportive evidence for HIV patients to start regularly exercising, particularly within the early stages of the disease. However, others have noted that to date no convincing data exist that link moderate exercise training with improved T helper cell counts<sup>267</sup>. While this may be true, the potential role for exercise in maintaining cell counts rather than improving counts, should not go unnoticed or undervalued.

In summary, cross-sectional and epidemiological evidence now exists that demonstrates single acute exercise bouts and prolonged training can produce changes in the distribution and function of particular immune system components<sup>308</sup>. Despite some conflicting evidence, data collection to date has led to an extension of Nieman's J-shaped curve, to the development of the "inverted 'U' theory" that illustrates moderate exercise enhances immune function, while heavy or lack of exercise may attenuate the immune response<sup>308, 438</sup>. The development of this theory has raised the hope that a suitably graded exercise program might be a valuable adjunct to the prevention or treatment of cancer. Therefore, exercise and cancer studies have predominantly investigated the role of exercise in enhancing the innate immune system or the first line of defense.

In comparison, studies involving patients with HIV have predominantly assessed the role of exercise in enhancing T cells and have shown promising results. Furthermore, the beneficial immune changes observed have been related to an improved ability of the exercising patients to ward off latent viruses. It is known that for patients undergoing a PBST, T cells are usually the last cells to recover, often taking up to 6 months to return to 'normal' levels. It is also known that the risk of colds and infections is high among this patient population. Therefore, it seems plausible that if exercise could improve immune cell recovery following a PBST, in particular T cell recovery, the risk and presence of colds and infection could reduce during the recovery period.

## 6.2 Methodology

Chapter 3 provides a detailed outline of the methodological procedures that relate to subject recruitment, the testing phases and the intervention program implemented. In summary, 12 patients, with 6 patients in each group were recruited. Of these, only 7 patients were recruited at PI, while the remaining subjects entered the investigation at PII. Outlined below are the methodological procedures, which relate specifically to the aims of this section of the investigation and involve the assessment of T cell number and function.

Unlike the previous 2 study chapters that involved 3 testing phases, this study assesses T cell number and function at more frequent intervals and includes an additional 2 testing phases. These 2 testing phases are implemented at the end of the first and second month of the intervention period (I1 and I2, respectively). Therefore, T cell number and function are assessed at PI (pre-transplant), PII (post-transplant), I1 (1-month post-PII), I2 (2-months post-PII) and PIII (3-months post-PII).

### 6.2.1 T cell number and function

#### Blood sampling

Because lymphocytes exhibit a circadian rhythm<sup>446</sup>, blood sampling was set for all patients between 8-10am. In addition, since an acute bout of exercise can influence blood counts<sup>349</sup>, patients refrained from exercise participation for 24-hours prior to blood sampling.

A 10ml sample of blood was collected from the ante-cubital vein of the forearm during each of the 5 testing phases, using a winged cannula attached to an ethylene diaminetetra-acetic acid treated vacutainer. A commercial pathology service (S&N Laboratories) collected the blood samples for the study during routine blood tests, and was therefore able to provide full blood count data.

## Cryopreservation of the cells

For convenience of data analysis, the blood samples were cryopreserved prior to developing the assays and performing lymphocyte subset counts. Cryopreservation involved the separation of mononuclear cells from whole blood by “Ficoll-Hypaque” density centrifugation, which were then washed and suspended at room temperature in RPMI (Roswell Park Memorial Institute) 1640 supplemented with 20% heat-inactivated fetal calf serum. An equal volume of freezing medium (complete RPMI 1640 plus 15% dimethylsulfoxide (DMSO)) was added dropwise. This yielded a final freezing suspension of complete RPMI 1640 plus 10% foetal calf serum (FCS) plus 7.5% DMSO. This mixture was pipetted into ampoules and was then transferred to a controlled-rate freezer at  $-70^{\circ}\text{C}$ . The cells remained in the freezing medium for minimal time prior to being frozen.

At the time when the cells were required for the development of the proliferation assays, the cryopreserved cells were removed from the freezer and immediately and rapidly thawed by shaking in a  $37^{\circ}\text{C}$ -water bath. Prior to the last ice crystal being melted, the vial was removed from the water bath. With a 1ml pipette, the contents of the vial were transferred to a 15ml round tube by gently adding the cells down the side of the tube. The tube was then placed at room temperature and the dilution procedure to remove the DMSO was initiated. By using RPMI and human AB serum, the procedure began by gently adding 1 drop of complete medium down the side of the round-bottom tube. The addition was then repeated, doubling the volume each time (that is, 2, 4, 8, 16, 32 drops, etc) until a DMSO concentration of 4% was achieved. Following each addition, the cells and medium were gently mixed. The round-bottom tube was filled to a 15ml volume with medium, and then centrifuged at 200g for 10 minutes. Aspiration of the medium followed. The cells were then resuspended in complete RPMI with 10% foetal calf serum, at a concentration of  $8 \times 10^5 \text{ cell.ml}^{-1}$ .

### Lymphocyte proliferation assays

Aliquots of 200 $\mu$ l were added to round-bottomed microtitre 96-well plates at a final concentration of 20 $\mu$ gml<sup>-1</sup>. Eight replicates of cultures with mitogen (positive wells) and eight replicates of cultures with phosphate buffered saline (PBS) added instead of mitogen (controls/blank wells), were then incubated at 37°C in a 5% CO<sub>2</sub> humidified atmosphere for 64 hours. Following incubation, the culture media was carefully removed with a multi-channel pipette, ensuring that the cells were not disturbed from the bottom of the plate. The culture was then replaced with fresh, serum-free RPMI (100 $\mu$ l per well).

Colorimetric detection methods were utilised to quantify cell number and proliferation rates of human T cells. To each well, 10 $\mu$ l of MTT (3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) at 5mg/ml in PBS was added and incubated for 4-6 hours (37°C in 5% CO<sub>2</sub>). MTT is converted to intensely coloured (blue) formazan products by mitochondrial enzymes. These products can be detected spectrometrically at an absorbance of 540nm. Following the incubation period, 150 $\mu$ l of acid isopropanol (3.32ml concentrated HCl in 1 litre isopropyl alcohol - 0.04M HCl) was also then added and the plate was left at room temperature for approximately 60 minutes to assist the crystals to dissolve. Each well was then mixed by pipetting up and down with a multi-channel pipette. Finally absorbance was read at 540nm, and adjusted for background absorbance, which was read at 630nm.

Throughout the literature the quantification of cell function occurs in two ways:

- **Method 1:** *positive minus the blank (unproliferative cells)* – the absorbance obtained from the blank wells is taken away from the absorbance obtained from the positive wells.
- **Method 2:** *positive* – this method involves the measurement of the absorbance obtained from the positive wells only and ignores the absorbance obtained from the blank wells.

Previous research has demonstrated that there is no difference between the results obtained from both methods<sup>70</sup>. Therefore, as a consequence of dealing with low cell

counts in this investigation, method 2 was implemented. That is, during some of the testing phases, particularly at PII, the number of cells available for the assay enabled the development of positive wells only. During these testing phases, the latter method enabled the attainment of results, even when cell numbers were low.

Furthermore, since mitogens are known to stimulate specific lymphocyte subsets<sup>70</sup>, it has previously been suggested that mitogen responses should be expressed on a per cell basis of the major respondent subset. In the case of the mitogen used for this assay, that subset is T lymphocytes (CD3+ cells). Moreover, it is generally accepted that it is the T helper cells (CD4+ cells) which respond to the mitogen, rather than the CD8+ cells. Therefore, once function was quantified, the data were adjusted according to the number of CD3+, and also according to the number of CD4+ cells, present within the well. Total blood counts and lymphocyte subset counts were therefore required.

### **Lymphocyte subset counts and total blood counts**

Following lymphocyte suspension at a concentration of  $8 \times 10^5$  cell.ml<sup>-1</sup>, and prior to the development of the assay, 50µL of cells was mixed with 5µL of a cocktail of selected monoclonal antibodies conjugated with fluorescein isothiocyanate (FITC), phycoerythrin (PE), and peridin chlorophyll-a protein (PerCP) in the following combinations: CD3 monoclonal were conjugated with PerCP, CD4 monoclonal with FITC, and CD8 monoclonal with PE. Monoclonal antibodies were purchased from Becton-Dickinson, San Jose, CA, USA. Following a 30-minute incubation period in the dark, cells were then washed with PBS, then resuspended in 200µL of 2% paraformaldehyde solution. Stained cells were passed through a Becton Dickinson FACScan flow cytometer and were specifically gated. The same forward- and side-scatter parameters were used for each trial as established for human peripheral leucocytes. Standard gating procedures were used to select mainly lymphocytes and to differentiate between labelled and unlabelled cells. The natural fluorescence of unstained preparation and its contribution to the fluorescence channels was determined using an unstained proportion of the cell suspension. Once the CD3+ cells were gated, the CD4+ and CD8+ subsets were then gated from this identified CD3+ population. Full blood counts (provided by S&N Laboratories) taken at the

same time as the blood sample, were then used in conjunction with the data collected via the use of the FACScan, to determine absolute CD3+, CD4+ and CD8+ counts.

Therefore, data were obtained for:

- leucocyte and lymphocyte counts,
- T cells (CD3+) and T cell subset counts (CD4+ and CD8+ counts),
- and T cell function, which was expressed in three ways:-
  - positive (positive response to mitogen only);
  - positive/absolute number of CD3+ cells;
  - and, positive/absolute number of CD4+ cells.

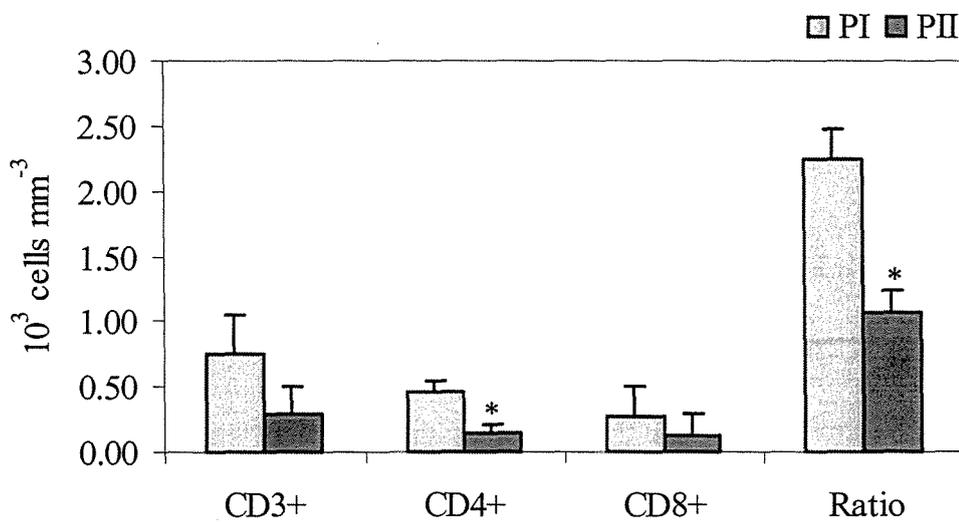
### **6.2.2 Statistical analysis**

Data for T cell numbers and function were analysed according to the statistical procedures outlined in Chapter 3.

### 6.3 Results

As shown in Figure 6.2, undertaking a PBST is associated with adverse effects on T cell subsets, with CD4+ cells and the CD4+/CD8+ ratio illustrating significant declines.

**Figure 6.2** T cell subset measures at PI and PII for the study group (mean±SE)



n = PI-7, PII-10

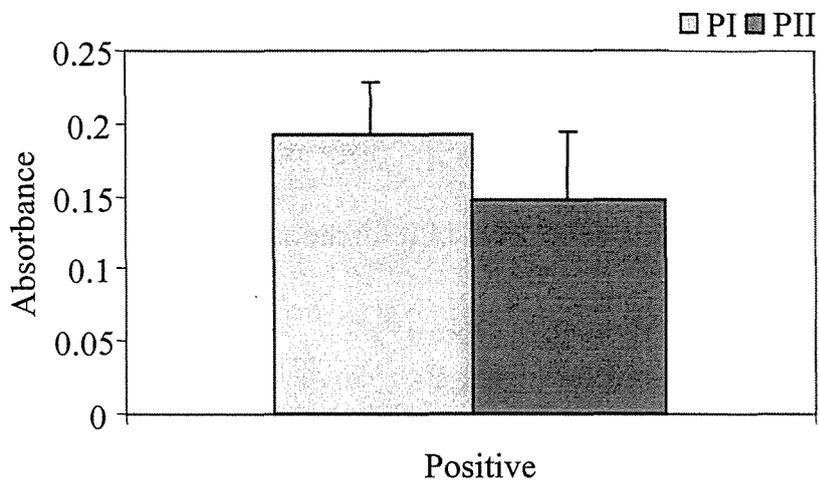
\* p<0.01

Figures 6.3a and b, depict the change in T cell function caused by the PBST.

While the mean total T cell function (total positive response, Figure 6.3a) declined, function per CD3+ cell and per CD4+ cell (Figure 6.3b) increased. However, the changes were not significant.

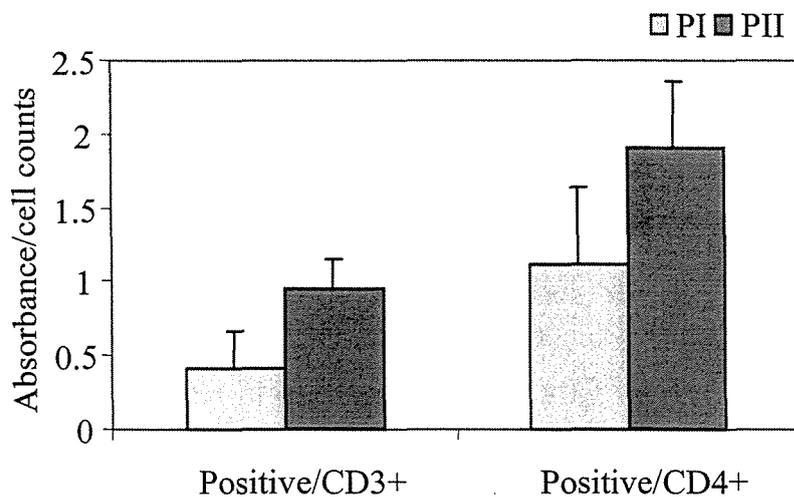
**Figure 6.3** T cell function at PI and PII for the study group (mean $\pm$ SE)

(a) Total positive response to the mitogen



n=PI-7, PII-11

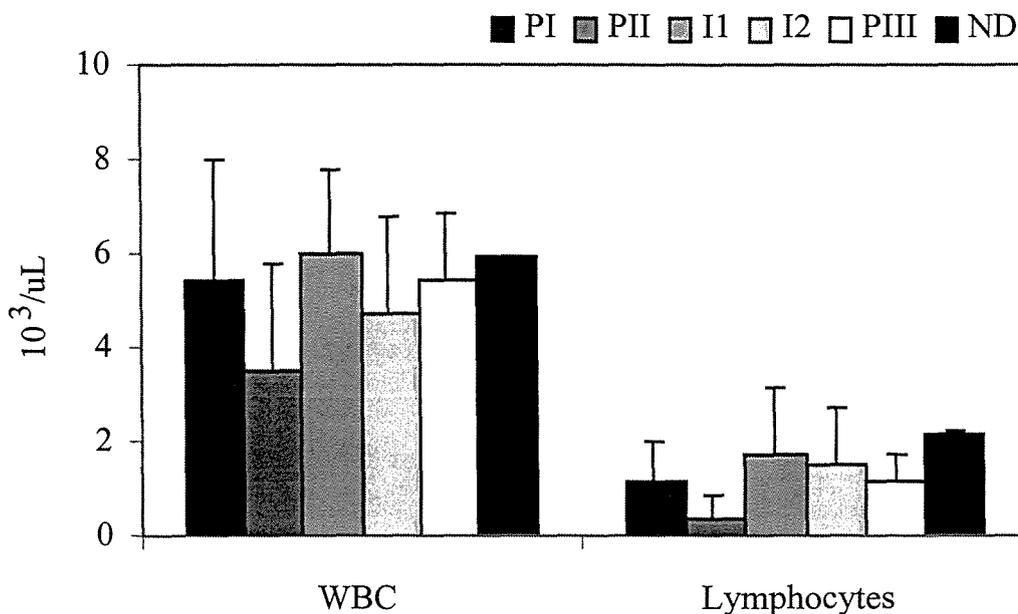
(b) Positive response to the mitogen, adjusted for CD3+ and CD4+ counts



n=PI-7, PII-8

Statistical analysis revealed that exercise had no effect on T cell count recovery following the transplant. This was evident by the p values calculated in the analysis of the group interaction for CD3+, CD4+ and CD8+ counts ( $p = 0.948, 0.777$  and  $0.870$ , respectively). Therefore, the CG and EG data were pooled for all testing phases and the means, standard deviations and standard errors, have been calculated for the entire group. Figure 6.4 illustrates that the white blood cell (WBC) counts significantly decreased following the transplant ( $p < 0.05$ ), but returned to pre-transplant and 'normal' age-matched levels by the end of the first-month post-transplant. Lymphocyte counts also declined significantly ( $p < 0.05$ ) by PII but significantly increased during the 1<sup>st</sup> month post-transplant ( $p < 0.01$ ). By I1, lymphocyte counts were similar to pre-transplant and age-matched levels.

**Figure 6.4** WBC and lymphocyte counts across the phases for the study group (mean $\pm$ SD)



n=PI-7, PII-11, I1-10, I2-10, PIII-9

ND = Age-matched normative data<sup>152</sup>

ND – WBC: median = 5.9, range = 4.6-7.1

Lymphocytes: median = 2.1, range = 1.6-2.4

Significant differences between phases and ND:

WBC: NDvsPII,  $p < 0.05$

Lymphocytes: NDvsPI & PIII,  $p < 0.05$ ; NDvsPII,  $p < 0.01$

Significant differences between phases:

WBC: PIIvsI1,  $p < 0.05$

Lymphocytes: PIIvsPI & PIII,  $p < 0.05$ ; PIIvsI1 & I2,  $p < 0.01$

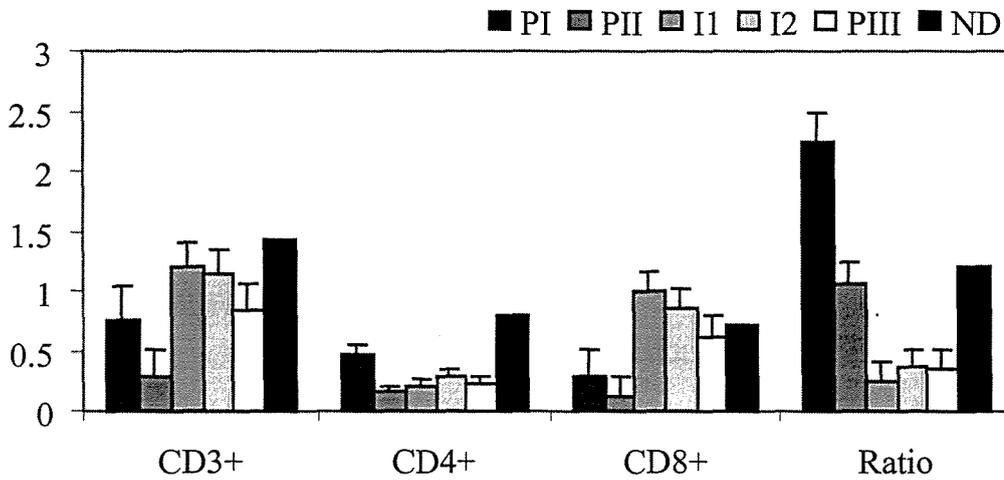
Figure 6.5a displays the changes in CD3+, CD4+, and CD8+ cell counts and the T cell ratio, across the phases. Also shown in Figure 6.5a are the comparable age-matched data for T cell subsets and ratios. Pre-transplant, CD3+ cell counts were significantly lower than age-matched healthy counts ( $p < 0.01$ ), and reduced further following the transplant. However, by 1-month post-transplant, CD3+ counts had significantly increased ( $p < 0.05$ ) and were similar to healthy matched controls. Counts remained at 'normal levels' for another month, but by 3-months post-transplant, declined to levels that were again significantly lower ( $p < 0.01$ ) than age-matched data.

CD4+ counts declined ( $p < 0.01$ ) by PII, and showed little improvement throughout the testing phases. As can be seen by Figure 6.5a, CD4+ counts were significantly lower than age-matched data at all testing phases.

At PI, absolute numbers of suppressor T cells (CD8+) were lower ( $p < 0.01$ ) than age-matched data and undertaking the transplant was associated with a further mean decline. However by I1, counts had increased ( $p < 0.05$ ) to levels that were similar to normative data. Although suppressor counts illustrated a decline between I1 and PIII, counts remained similar to normative values.

The ratio between the helper to suppressor cells dropped following the transplant ( $p < 0.01$ ) and continued to decline until the end of the first-month post-transplant. At I1, the ratio was significantly less than pre-transplant and 'normal' levels ( $p < 0.01$ ). While the ratio showed a mean increase between I1 and PIII, at the end of the intervention period, the ratio remained lower than pre-transplant and normal ( $p < 0.01$ ) levels. Individual T cell ratio measures across the testing phases for 2 subjects are displayed in Figure 6.5b. These 2 patients were followed for a longer period post-transplant, and demonstrated that at 4-months post-transplant the ratio remained low (0.45 for one patient, and 0.15 for the other). Additionally, one subject was followed for another one-month and reported a ratio of 0.16 at 5-months post-transplant.

**Figure 6.5(a)** T cell subset and T cell ratio measures across the phases for the study group, and comparisons with normative data (mean±SE)



n=PI-7, PII-10, I1-10, I2-10, PIII-9

Absolute Counts are expressed in  $10^3$  cells  $mm^{-3}$

ND =Age-matched normative data<sup>152</sup>

ND - CD3+: median = 1.4, range = 1.1-1.7

CD8+: median = 0.7, range = 0.5-0.9

CD4+: median = 0.8, range = 0.7-1.1

Ratio: median = 1.2, range = 1.0-1.5

Significant differences between phases and ND:

CD3+: NDvsPI, PII & PIII,  $p < 0.01$

CD4+: NDvsPI, PII, I1, I2 & PIII,  $p < 0.01$

CD8+: NDvsPI, & PII,  $p < 0.01$

Ratio: NDvsI1, I2 & PIII,  $p < 0.01$

Significant differences between phases:

CD3+: PIIvsI1 & I2,  $p < 0.05$

CD4+: PIVsPII,  $p < 0.01$ ; PIVsI1 & PIII,  $p < 0.05$

CD8+: PIIvsI1 & I2,  $p < 0.05$

Ratio: PIVsPII, I1, I2 & PIII,  $p < 0.01$ ; PIIvsI1, I2 & PIII,  $p < 0.05$

**Figure 6.5(b)** Individual T cell ratio measures across the phases for 2 subjects at PI, PII, I1, I2, I3 (3-months post-PII), I4 (4-months post-PII) and I5 (5-months post-PII)

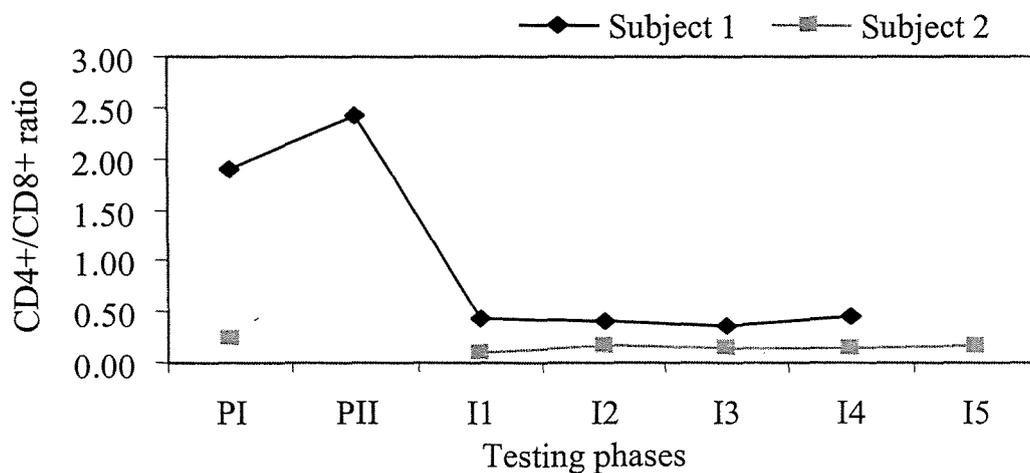
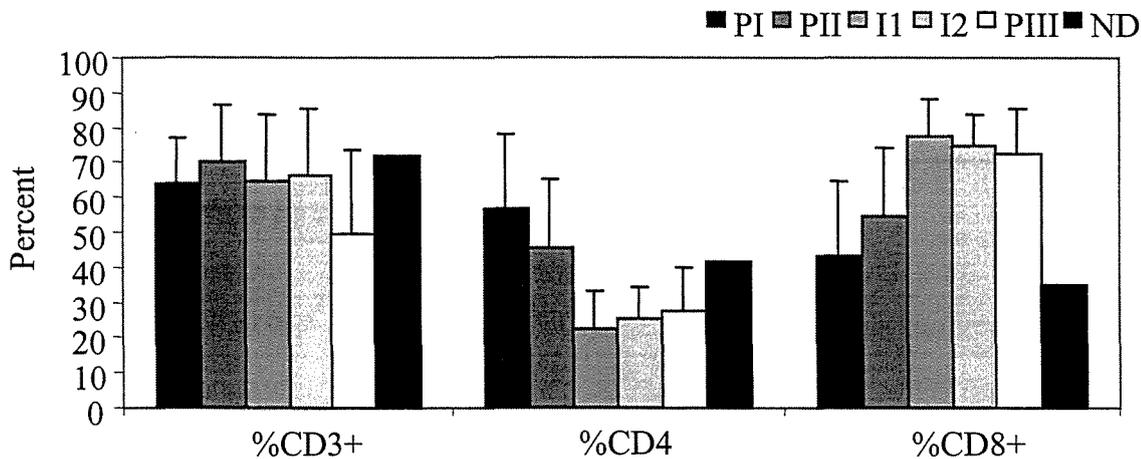


Figure 6.6 illustrates the changes in T cell subset percentages across the phases and compares study group data with age-matched normative data. The percentage of CD3+ cells remained relatively stable up until the 3<sup>rd</sup>-month post-transplant (PIII). Until this time, the percentage of lymphocytes that were CD3+ cells was close to normative data. However, by PIII, the percentage of CD3+ cells was lower ( $p<0.05$ ) than age-matched data. The percentage of CD4+ cells decreased ( $p<0.05$ ) following the transplant and continued to decline until I1. The percentage of CD4+ cells was significantly lower at I1, I2 and PIII when compared with pre-transplant ( $p<0.01$ ) and age-matched data ( $p<0.01$ ). Furthermore, %CD8+ cells increased between PI and PII ( $p<0.05$ ) and continued to increase until I1 ( $p<0.01$ ). At I1, the percentage of suppressor cells was higher than pre-transplant levels ( $p<0.01$ ) and normative data ( $p<0.01$ ) and remained at those levels until the end of the intervention period.

**Figure 6.6** T cell percentages across the testing phases for the study group, and comparisons with normative data (mean±SD)



n=PI-7, PII-10, I1-11, I2-12, PIII-11

ND = Age-matched normative data<sup>152</sup>

ND - %CD3+: median – 72, range – 67-76

%CD4+: median – 42, range – 38-46

%CD8+: median – 35, range – 31-40

Significant differences between phases and ND:

%CD3+: NDvsPIII,  $p<0.05$

%CD4+: NDvs I1, I2 & PIII,  $p<0.01$

%CD8+: NDvsPII,  $p<0.05$ ; NDvsI1, I2 & PIII,  $p<0.01$

Significant differences between phases:

%CD3+: PIIIvsPI & I1,  $p<0.05$ ; PIIIvsPII & I2,  $p<0.01$

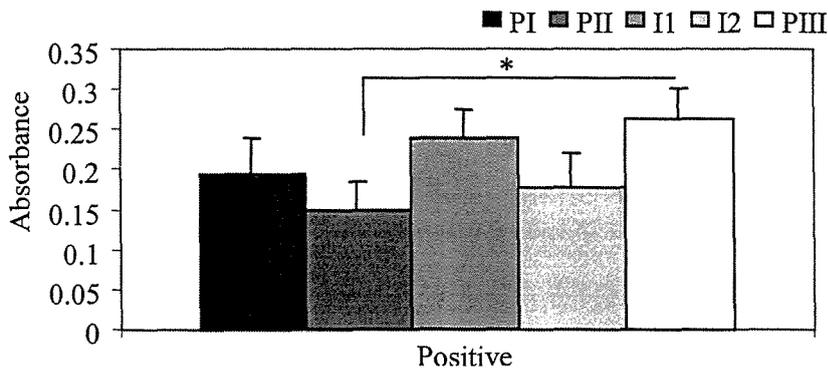
%CD4+ & %CD8+: PIvsPII,  $p<0.05$ ; PIvsI1, I2 & PIII,  $p<0.01$

PIIvsI1, I2 & PIII,  $p<0.01$

Statistical analysis revealed that the intervention program had no effect on T cell function recovery following the transplant. This was evident by the p values calculated in the analysis of the group interaction for T cell function, expressed as the positive response to the mitogen, positive response adjusted for CD3+ cells and the positive response adjusted for CD4+ cells ( $p = 0.861, 0.200$  and  $0.135$ , respectively). Therefore the subject data from the control and exercise group were pooled. Figure 6.7 depicts the changes in T cell function, expressed as the total positive response only (Figure 6.7a), positive response per CD3+ cell (Figure 6.7b), and positive response per CD4+ cell (Figure 6.7b), across the testing phases. T cell function was significantly higher at 3-months post-transplant, when compared with immediately post-transplant, when expressed as the total positive response. However, no other changes in function across the phases were significant, regardless of how function was expressed.

**Figure 6.7** T cell function across the testing phases for the study group (mean+SE)

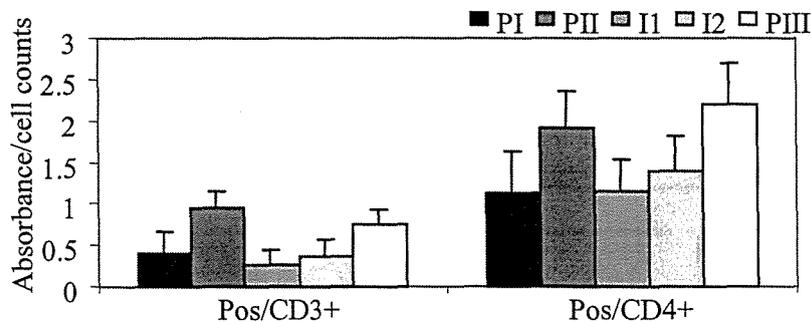
(a) Total positive response to the mitogen



n=PI-7, PII-11, I1-11, I2-9, PIII-11

\*  $p < 0.05$

(b) Positive response to the mitogen, adjusted for CD3+ and CD4+ counts



n=PI-7, PII-8, I1-9, I2-8, PIII-9

## 6.4 Discussion

The results of this investigation demonstrated that while the absolute WBC count, percentages of CD3+, CD4+ and CD8+ cells and the CD4+/CD8+ ratio were considered normal pre-transplant, the absolute counts of lymphocytes and T cell subsets were below age-matched controls. Therefore, patients were already immunocompromised prior to undertaking a PBST. Following the transplant, adverse changes were observed for total leucocyte, lymphocyte, CD3+, CD4+, and CD8+ counts, and the helper/suppressor ratio. Regardless of whether an exercise program was initiated post-transplant, more than 3-months was required for total lymphocyte and T cell subset counts to return to 'normal' levels. Additionally, T cell function was adversely affected following the transplant but showed a mean improvement during the 3-months post-transplant. However, these changes were not statistically significant.

### 6.4.1 Pre-transplant immune parameters

Until now, little data have been available regarding pre-PBST immune function, and it was therefore difficult to determine the exact impact of undertaking a PBST on immune parameters. Additionally, immunological measurement pre-transplant allows the quantification of immune status in cancer patients who are likely to have undergone previous conventional treatment regimens. Previous research has associated a deterioration in immune status and function with cancer<sup>51, 190, 356</sup> and its associated treatment<sup>53, 393</sup>. Therefore, the patients investigated within this study were considered 'at risk' of maintaining poor immune status, even prior to undertaking a PBST.

While the percentage of lymphocytes that were T cells, and the percentage of T cells that were CD4+ and CD8+ cells at PI, were similar to normative data, absolute counts for T cells, helper T cells and suppressor T cells were below 'normal' ( $p < 0.01$ ). In addition, although the mean helper/suppressor ratio for the study group was considered normal, an analysis of individual ratios demonstrated that 2 out of 7 patients assessed pre-transplant, were experiencing below 'normal' ratios. Furthermore, total lymphocyte counts were also below normative ranges and can be

used to explain how the percentage of CD3+ cells were considered normal while the absolute count was not. Although total leucocytes were slightly less than age-matched normative data, the difference was not significant. Through the analysis of the full blood counts, it was determined that leucocytes other than lymphocytes, such as neutrophils, monocytes, eosinophils and basophils, were able to recover following previous treatment to levels which enabled the total WBC count to reach near normal levels.

As discussed earlier, T cell function was determined in three ways. Firstly, via quantification of the positive response to the mitogen, secondly by dividing the positive mitogen response by the absolute number of CD3+ cells, and finally, by dividing the positive mitogen response by the absolute CD4+ cell count. When it is assumed that CD4+ cells are predominantly proliferating in response to a mitogen, then expression of function per CD4+ cell would be considered the most appropriate. However, if it were assumed that both CD4+ and CD8+ cells show a proliferative response in the presence of a mitogen, then expression per CD3+ cell would be considered the most appropriate method. More work is required before either of these assumptions can be fully accepted. Nevertheless, regardless of how function was expressed, mitogen response observed at PI, compared with the mitogen response observed by other work performed on cells from 'healthy' subjects within the QUT laboratories, was not significant. These comparisons indicate that the lymphocytes were functioning at below 'optimal' levels pre-transplant, with the results providing support for the statement, that "lowered T cell function has been considered a hallmark of malignant disorders"<sup>356</sup>.

The quantification of these immune parameters indicates that cancer, prior treatment or factors associated with cancer diagnosis and treatment - such as treatment-related physical inactivity, psychological stress, or a change in food intake - have led to a deterioration in lymphocyte and specifically T cell counts, and T cell function. That is, the adaptive component of the immune system, which has a primary role in preventing the presence of illness or infection, is compromised pre-transplant. Further, any negative impact that the transplant is likely to impose will exacerbate cancer patients' already 'poor' immune status.

#### 6.4.2 The impact of a PBST on T cell number and function

Irradiation and some cytostatic drugs elicit a steep dosage-versus-antitumour effect relationship, with a correlation existing between the higher the dose, the more effective eradication of the malignant cell. However, due to the toxicity of normal tissues such as the bone marrow or gastrointestinal epithelium, dosage escalations above 150-250% of the conventionally used dosages of drugs are prevented, and therefore CT doses are often insufficient to cure specific cancers<sup>250, 397</sup>. Failure to find exploitable differences between malignant and normal cells have frustrated the attempts to develop more effective agents that would allow the highly selective therapy required for tumour eradication. However, the inability to use drugs to eradicate the tumour without being lethal to the patient has led to the development of PBST. The transplantation process begins with an intensive course of high-dose CT, called the 'conditioning regimen'. Following high-dose CT, patients are 'rescued' from the lethal effects of the treatment with their previously collected pluripotent stem cells<sup>126</sup>. These stem cells are able to migrate to the bone marrow and immediately begin their role of generating one or more subsets of mature cells that eventually evolve into erythrocytes, leucocytes or platelets. Following this conditioning regimen, a period of profound pancytopenia<sup>371</sup> is inevitable.

As was expected, the patients in the study demonstrated a mean decrease in leucocytes, T cells and suppressor cells, in addition to a significant decrease in the total lymphocyte count, CD4+ cell count, and the helper/suppressor cell ratio. By PII, leucocyte, lymphocyte, CD3+, CD4+ and CD8+ cell absolute counts were lower than age-matched normative data. In contrast, the mean ratio of helper to suppressor cells was similar to age-matched data during this same testing phase. However, unlike the other immune parameters measured, the helper/suppressor ratio was on average higher than age-matched data at PI. Additionally, an analysis of individual ratios showed that only half of the group assessed at PII reported ratios similar to age-matched controls, while the remaining 5 subjects reported below normal ratios. The mean leucocyte and lymphocyte counts at PII were  $5.46 \pm 2.47$  and  $0.38 \pm 0.47 \times 10^3$  x cells/ $\mu$ L, respectively. While the leucocyte counts of the PBST patients were

similar to stage I and II breast cancer patients ( $5.25 \pm 2.08 \times 10^3$  cells/ $\mu\text{L}$ )<sup>293</sup>, the lymphocyte counts were much lower ( $1.49 \pm 0.69 \times 10^3$  cells/ $\mu\text{L}$ )<sup>293</sup>.

Additionally, a PBST leads to a reduction in the mean total positive response to the mitogen. In contrast, the mean function per CD3+ cell and per CD4+ cell is elevated. When these results are considered concurrently they indicate that while function per CD3+ and CD4+ cell was enhanced, total function was reduced. Irrespective of the manner in which function was expressed, the changes were not significant and therefore the results indicated that undergoing a PBST had no impact on an already below optimal T cell function. In comparison, previous research has demonstrated impairment in T cell function following a PBST or BMT transplant<sup>384</sup>.

The results indicate that a patient who has undergone a PBST is in an immunocompromised state immediately post-transplant, with both the innate and adaptive components of the immune system being adversely effected. Consequently, these patients are considered to be at an elevated risk of infection post-transplant<sup>371</sup>. Therefore, PBST patients are often advised to avoid public places or environments with crowds or children and are also given recommendations regarding safe food preparation. Patients are expected to follow these guidelines until their immune system has fully recovered and yet previous research has demonstrated that T cells can take up to 6 months to recover<sup>384</sup>. Unfortunately, these guidelines may have certain social and psychological ramifications for the patient which, in turn, could potentially lead to the release of immunomodulatory hormones. What is unknown at this stage, but is of clinical interest, is the difference between infection rates of patients who do and do not comply with these recommendations.

### 6.4.3 Changes in immune parameters post-transplant

Statistical analysis revealed that there was no group-by-phase interaction, indicating that the exercise intervention did not influence the recovery of cells post-transplant. Therefore, the results obtained from the CG and EG were pooled.

While leucocyte counts were below normal following the transplant, by I1 counts had significantly increased and had returned to what were considered normal levels. Additionally, lymphocyte counts during this same period also showed a significant increase by I1, and reached numbers similar to age-matched data. The increase in lymphocyte counts during PII to I1 can account for some of the elevation in WBC counts during the same period. However, by 1-month post-transplant, the full blood count analysis revealed that neutrophils and monocytes had also fully recovered for all patients. Therefore the increase in neutrophils, monocytes and lymphocytes all attributed to the elevation in total leucocyte counts by I1. Previous research has also demonstrated that neutrophils<sup>371</sup>, monocytes<sup>384</sup> and NKC<sup>337, 384</sup> are able to recover within 1-month following a PBST.

While leucocyte counts showed a mean decrease by I2, followed by a corresponding mean increase by 3-months post-transplant, the fluctuations were not significant and values remained within normal ranges. Lymphocyte counts demonstrated the same trend between I1 and I2, but again the changes were not significant. However, in contrast to WBC, following I2, a mean decline in lymphocyte counts was observed. By 3-months post-transplant, although the mean lymphocyte count was significantly higher than that measured at PII, counts remained significantly lower than age-matched data. The results indicate that more than 3-months is required for total lymphocytes to fully recover following a PBST. An analysis of change across time for specific lymphocyte subsets (CD3+) provided more detail regarding the factors contributing to these changes.

The trend across time for the mean change in CD3+ counts is similar to that observed for the total lymphocyte count, in that CD3+ counts significantly increased during the first month post-transplant and reached levels considered normal. However, during this same period, the %CD3+ population demonstrated a mean decrease. By taking into account changes in lymphocyte and T cell percentage and absolute numbers, the results indicated that NKC experienced a faster recovery following the transplant, when compared with the recovery rates of T cells. Again, these results support those previously reported<sup>384</sup>. Between the 1<sup>st</sup>- and 2<sup>nd</sup>-month post-transplant, a mean decline in absolute CD3+ counts was observed, followed by a further decline by the 3<sup>rd</sup>-month post-transplant. At PIII, T cell counts had returned to levels that

were significantly less than age-matched counts. It seems plausible to suggest that the change in the mean absolute CD3+ count following the transplant could account for some of the change observed in the mean total lymphocyte counts during the recovery period. In addition to these results, by PIII, the %CD3+ cell population was lower than pre-transplant, post-transplant and normative percentages. In order to explain these results, an analysis of CD4+ and CD8+ data are required.

The percentage of T cells that were CD4+ cells and CD8+ cells, significantly decreased and increased, respectively, between PII and I1. A mean increase and thus a corresponding mean decrease, for the percentages of helper and suppressor cells, respectively, were observed between I1 and PIII. By PIII, the percentage helper cell population was significantly less than normal, while the percentage suppressor cell population was significantly higher than normal. It is therefore likely that the drop observed in the %CD3+ population between I2 and PIII, was a consequence of the significantly lower than normal %CD4+ cell population during this same period.

The suppressor cells recovered at a faster rate than the helper cells, as can be seen by the significant increase in CD8+ cells between PII and I1. The CD8+ counts then demonstrated a mean decline from 1-month to 3-months post-transplant, but during this period remained similar to age-matched controls. Further, by 3-months post-transplant, CD8+ counts were also similar to pre- and immediately post-transplant measures. These results are supportive of previous research findings<sup>158, 384</sup> that demonstrated high levels of suppressor cell activity following transplant, which then returned to pre-transplant levels by day 100.

As previously mentioned, CD4+ counts declined significantly following the transplant and remained significantly lower than pre-transplant and normative data at 3-months post-treatment. Furthermore, the results obtained from 1 patient followed for 4-months post-transplant, and another followed for 5-months post-transplant, demonstrated that the CD4+ cell population was still unable to recover by 4-5 months post-transplant. Previous investigations have also found that CD4+ cell counts may take up to 6 months to fully recover post-transplant<sup>158, 384</sup>.

T cell ratio changes are a direct consequence of the CD4+ and CD8+ cell count changes. However, unlike the other immune parameters assessed within this investigation, the mean helper/suppressor ratio for the group, did not fall below normal until 1-month following the transplant. This trend was evident in over half of the subjects within the study group. However, 2 subjects demonstrated below normal ratios at PI, and maintained a low ratio throughout all testing phases. While this mean group ratio showed a slight increase from I1 to PIII, 3-months post-transplant the ratio ( $0.42 \pm 0.26$ ) remained significantly lower than pre-transplant and age-matched values. Furthermore, the 2 subjects followed for an additional 1 month, and 2 months post-transplantation demonstrated the continued maintenance of below normal helper/suppressor ratios. Others have also reported a mean helper/suppressor ratio of  $0.3 \pm 0.2$  within the first 3-months post-transplant<sup>158</sup>. The low ratio relates to an imbalance of the adaptive component of the immune system, which can potentially lead to adverse implications for the cytokine cascade that activates other immune cells<sup>349</sup>. In particular, NK cell cytotoxicity is potentially reduced as a consequence of a deficiency in interleukin-1 and interferon-gamma, and/or the activation of suppressor mechanisms.

Major increases in susceptibility to either infection or spontaneous neoplasia are considered unlikely while the ratio exceeds 0.2<sup>34</sup>. However, others have noted that susceptibility to infection is elevated if the ratio falls below 1.5<sup>191</sup>. Normative values for the CD4+/CD8+ ratio for the 18-70 year age group have been reported as 1.2<sup>152</sup>. Therefore, while the patient population presented in this investigation maintained ratio values above 0.2, the mean ratio by 3-months post-transplant was approximately one third of age-matched 'normal' ratios and approximately one quarter of 1.5. Without comparing infection rates post-transplant to healthy matched controls, it is inappropriate to suggest that these patients, by nature of the low helper/suppressor ratio, were at an elevated risk of infection. It seems evident that the clinical significance of the helper-to-suppressor ratio needs further investigation before a specific ratio value becomes accepted as the critical level for elevated risk of infection. Additionally, when evaluating risk of infection, it is also relevant to consider changes in cell function, along with changes in cell counts.

In general, small and insignificant changes were observed in function during the recovery period. Nevertheless, by 3-months post-transplant, the mean function (regardless of how it was expressed) was higher than function measured immediately following the transplant. Furthermore, the change between the total T cell function at PII and PIII was significant. However, at the end of the testing phases, function was similar to pre-transplant measures, and as has already been discussed, pre-transplant function was considered below normal. These results provide support for previous work, which has demonstrated an impairment in T cell function in patients who have undertaken PBST or BMT<sup>384</sup>.

#### **6.4.4 The role of exercise in immune system recovery**

It was an objective of this investigation to assess the chronic exercise effect on immune parameters rather than the acute effect. The results of this study demonstrated that 3-months of regular exercise following a PBST, had no influence on immune cell recovery. Others have also shown that an 8-week exercise program failed to significantly enhance the NKC function, or NKC and T cell counts of patients with breast cancer<sup>261</sup>. In contrast, improved NKC activity has been demonstrated in breast cancer patients following participation in a 7-month exercise intervention program<sup>292</sup>. It therefore seems plausible that a longer intervention may be required to observe differences in immune status and function, between exercising and control patients. However, others have shown significantly higher NKC activity levels in exercising patients with stomach cancer following a 14-day moderated exercise program when compared with controls. Variations in the cancer populations studied, the treatments regimens undertaken, the timing of the intervention, the exercise programs implemented, and initial immune parameters are likely factors that have contributed to the results observed in the above studies, and make comparisons between the studies difficult. Nevertheless, it is evident that work regarding the chronic exercise effect on immune parameters in cancer patients is limited and preliminary, and requires further research.

It could also be suggested that the exercise intervention implemented in this study was not of sufficient magnitude to induce an effect. However, the previous chapters have clearly outlined the benefits attained in body composition, energy expenditure,

aerobic capacity and muscular strength by the exercising subjects. Gains in aerobic fitness, in the absence of changes in total leucocytes, lymphocytes, or CD4+ and CD8+ subsets, have also been found in patients with HIV<sup>319</sup>. These results indicate that while certain physiological improvements can be observed within 3-months, other physiological components may require a longer period.

## **6.5 Conclusion**

In summary, the PBST patients were already immunocompromised prior to undertaking the transplant and the transplant procedure imposed further adverse changes to WBC and lymphocyte counts. Participation in the exercise program had no impact on immunological changes following treatment. White blood cell and CD8+ cell counts returned to normal within 3-months post-transplant, however the lymphocyte, CD3+, and CD4+ cell counts demonstrated a delayed recovery for both exercising and non-exercising patients. Although participation in the exercise program had no influence on immune cell recovery following a PBST, importantly immune recovery was not adversely effected, demonstrating that exercise participation was of no detriment to immune status and function for these patients.

# CHAPTER SEVEN

## STUDY FOUR

### **Changes in bone turnover following a PBST and participation in an exercise program**

*“Bone is laid down where needed and resorbed where not needed”  
Wolff's Law (1892)*

**List of abbreviations specific to Chapter seven**

4-NPO	4-nitrophenoxide
4-NPP	4-nitrophenylphosphate
BMC	Bone mineral content
BMD	Bone mineral density
BMT	Bone marrow transplant
CG	Control group
DXA	Dual energy x-ray absorptiometry
EG	Exercise group
GVHD	Graft versus host disease
PBM	Peak bone mass
PBST	Peripheral blood stem cell transplant
PI	Phase I
PICP	carboxyl-terminal propeptide of type I procollagen
PII	Phase II
PIII	Phase III
sAP	Serum alkaline phosphatase
SD	Standard deviation
SG	Study group
uDPyr/Cr	Urinary deoxypyridinoline/creatinine
uHP/Cr	Urinary hydroxyproline/creatinine

## **7. Changes in bone turnover following a PBST and participation in an exercise program**

---

### **7.0 Introduction**

As medical technology has advanced, outcomes have improved for many malignancies, and thus survival rates for those diagnosed with cancer are progressively increasing each year. Further, as survival rates continue to rise, there is an increasing concern over the quality of life of these patients<sup>16</sup>. Many of the side effects associated with cancer and treatment arise in the relatively early stages of the cancer continuum, and their immediate effects on physical function and quality of life are evident. However, certain side effects also exist, which may not influence function or quality of life until later in life. Bone turnover change induced by cancer, or treatment, inadequate nutrition or physical inactivity associated with cancer, is one such side effect that maintains the potential to influence function and quality of life in the longer term.

Bone turnover changes observed in patients with cancer relate to an elevation in bone loss and a corresponding increase in the risk of osteoporosis. The incidence of osteoporosis and consequential hip fractures is associated with high personal and community costs, particularly in developed countries. Mortality following hip fracture is in the order of 5-15%, while almost 50% of individuals become dependent following fracture<sup>218</sup>.

Participation in weight-bearing physical activity and resistance training has been shown to improve bone mineral density and reverse bone loss. However, the role of exercise on bone turnover in patients with cancer, has not been investigated. The recovery of cancer patients post-treatment should involve both the return to normal functioning and quality of life, as well as the prevention of conditions that could lead to an adverse effect on functional capacity and quality of life at a later stage. It seems plausible that participation in an aerobic and resistance training program throughout the cancer continuum could influence the rate of bone loss during

treatment and the ability to reverse bone loss following treatment. In turn, participation in exercise may therefore provide an important means of reducing the risk of osteoporosis, and therefore ultimately influence functional capacity and quality of life in the longer term.

### 7.0.1 Purpose

Objective 1: To investigate changes between pre- and post-PBST measures of bone turnover.

*Research hypothesis for objective 1:*

Bone turnover will increase following a PBST (as determined by pre- and post-transplant measures).

Objective 2: To investigate the role of a three-month duration, moderate intensity, mixed type exercise program on bone turnover, post-PBST.

*Research hypothesis for objective 2:*

Participation in the exercise program will lead to a beneficial effect on bone turnover, characterised by decreased resorption and increased bone formation activity (as determined by pre- and post-intervention measures).

## 7.1 Literature Review

Key determinants of skeletal status and the potential for fracture include peak bone mass (PBM) and the rate of bone loss<sup>282</sup>. The greater the PBM, the longer the period of bone loss that is required before the fracture threshold is reached<sup>116</sup>. Further, the maintenance of bone mass between the ages of 20 and 50 years is crucial to long-term skeletal health and can also influence the time at which the fracture threshold is reached<sup>82</sup>. Therefore, while most osteoporotic fractures occur in the elderly<sup>8</sup>, early life events which affect acquisition of PBM, length of time PBM is maintained, or rate of bone loss, can significantly influence the risk of osteoporosis in later life.

Although the essential morphology and biological processes of bone are predominantly genetically determined (60-80%)<sup>60</sup>, environmental and hormonal factors<sup>66, 198, 409</sup>, nutrition (specifically calcium intake)<sup>116, 236, 332</sup> and physical activity<sup>9, 184, 298</sup> also play an integral role and maintain the potential to alter the individual expression of this genetic potential<sup>60</sup>. However, prior to evaluating the effect of these factors on skeletal health, it is first important to understand how skeletal status is assessed.

### 7.1.1 Assessment of skeletal status

Two opposing activities, bone formation by osteoblasts and bone degradation by osteoclasts, characterise bone metabolism<sup>93</sup>. The tightly-coupled activity in time and space, in a sequence of events, defines a given remodelling unit<sup>112</sup>. Overall bone mass is dependent on the balance between degradation and formation within a remodelling unit and on the number of remodelling units which are activated within a given period of time in a specific area of bone<sup>93</sup>. Skeletal status can be assessed by either measuring bone mass (bone mineral content and bone mineral density) or by assessing the activity of osteoblasts or osteoclasts. Bone mass is assessed via the use of imaging techniques such as computed tomography, magnetic resonance imaging and more commonly, via the use of dual energy X-ray absorptiometry (DXA). The accuracy<sup>200, 408</sup> and repeatability<sup>238</sup> of using DXA to determine bone mineral content (BMC) and bone mineral density (BMD) make this a valid technique for assessing skeletal status. However, the ability to observe changes in BMC or BMD within a

relatively short period of time (less than 12 weeks) using DXA, or other imaging techniques, is limited due to the time required for the completion of a remodelling cycle (up to 200 days)<sup>113</sup>.

Osteoblast and osteoclast activity can be measured with biochemical markers. These markers are commonly categorised as markers of bone formation or resorption (Table 7.1).

**Table 7.1** Biochemical markers of bone turnover

Formation Markers:	Resorption Markers:
Osteocalcin (Gla protein of bone) (collagen and phosphatase crosslinks)	Pyridinoline and deoxypyridinoline
Total and bone-specific alkaline phosphatase	Total and dialysable hydroxyproline
Procollagen I extension peptide	Tartrate-resistant acid phosphatase
	Hydroxylysine glycoside
	Free $\gamma$ -carboxyglutamic acid
	Noncollagen protein fragments

A combination of markers can be implemented during the same period, making it possible to assess formation and resorption, and cell activity and matrix components, simultaneously. While the potential application of these markers is significant, limitations also exist. Technical problems include issues with storage life, precision, accuracy and sensitivity of the markers at low turnover rates of bone, and daily physiological fluctuations in the measurements being assessed. In addition, the markers are unable to distinguish between cell/tissue abnormalities and between trabecular, endosteal and cortical tissue sheaths<sup>378</sup>. While an ideal marker for bone formation and/or resorption does not exist<sup>93</sup>, these markers and combinations of markers have been extensively employed in bone turnover studies and have provided useful information.

The extent of new formation and bone degradation influences the biochemical parameters of bone metabolism. Bone stability occurs when equilibrium between formation and resorption exists<sup>378</sup>. This balance can be shifted in either direction,

favouring formation or resorption, depending on the environment or disease processes present.

### **7.1.2 Factors influencing skeletal status and risk of osteoporosis**

Osteoporosis has been defined as a “disease of the skeleton in which bone mass or density is reduced, accompanied by microarchitectural damage, such that there is an increase in the risk of fracture even in the absence of significant trauma”<sup>218</sup>. It represents a class of bone pathology where there exists an uncoupling of the processes of bone resorption and formation.

Osteoporosis usually develops with age, both as a result of the age-related decline of bone density (approximately 1%/year) coupled with the abrupt elevation in bone loss in females of up to 8% per year at the menopause<sup>60</sup>. Evidence stemming from investigations involving humans, primates and rodents has indicated that following loss of ovarian function, rate of bone resorption and formation elevate, with the former exceeding the latter<sup>230</sup>. In contrast, loss of bone that is specifically related to age is most likely a result of a reduction in the supply of osteoblasts in proportion to the demand for them. Age and postmenopausal bone loss also differ with respect to the skeletal sites affected. While postmenopausal bone loss predominantly occurs within trabecular bone, aging-associated bone loss primarily occurs in cortical bone<sup>230</sup>.

Other causes of bone loss exist and have been differentiated into categories relating to disease and drug therapy, diet and disuse<sup>279</sup>. The following review of the literature discusses the impact of each of these categories on skeletal status, and the presence of these factors in patients with cancer.

#### **7.1.2.1 Disease- and drug-related bone loss**

Numerous types of chronic diseases have been related to bone loss<sup>279</sup>, in particular those that require a patient to participate in the long-term use of specific drugs which induce bone loss as a side effect. Cancer is one such disease state and its treatment often involves the administration of drugs such as heparin, methotrexate,

cyclosporin, ifosfamide, and other steroids, which maintain the potential to adversely influence bone turnover. Unfortunately, the exact mechanisms of specific drugs are difficult to determine due to the disease process itself, and to the combination of several drugs implemented during the same period<sup>15</sup>.

Although the exact mechanism by which methotrexate influences bone turnover is unknown, an elevated urinary calcium excretion suggests that bone loss results from an increased bone resorption and excretion, rather than diminished bone formation<sup>188</sup>. With regard to corticosteroid treatment, osteoblast activity is reduced, as is the active life span of the osteoblasts<sup>15</sup>. The association between corticosteroid treatment and loss of bone is significant since fractures have been known to occur within weeks of the start of high-dose steroid therapy<sup>284</sup>.

A longitudinal investigation performed on children diagnosed with various cancers, including acute lymphocytic leukaemia, solid tumour, Ewing's sarcoma, rhabdomyosarcoma and neuroblastoma, demonstrated the effect of the disease process and the associated treatments on BMD<sup>157</sup>. The BMD analysis showed an already diminished BMD (below 1 standard deviation for the BMD at the hip or spine) at the start of treatment in 46% of the patients. These results suggested that the disease process itself may predispose patients to a reduced BMC. Twenty-five per cent of patients showed a drop of at least 0.5 standard deviation (SD) during chemotherapy (20% demonstrated a BMD decline of at least 1SD). Moreover, the investigation followed the children for at least 1-year and there was no consistent 'catch-up' response observed in BMD following treatment.

Additionally, age at diagnosis may have the potential to influence the ability to attain PBM, or the ability to maintain peak bone mass, prior to the 'normal' age-associated decline. Paediatric cancer and its treatments can have both direct (chemotherapeutic agents, glucocorticoids) and indirect (sex hormone deficiency, growth hormone deficiency, thyroid hormone treatment) effects on the skeleton that would be predicted to interfere with normal bone accretion<sup>8</sup>, while those diagnosed with cancer between the ages of 20-50 years are at risk of initiating bone loss at an early age.

Longitudinal changes in BMD, bone turnover and bone hormonal metabolism have been evaluated in children newly diagnosed with ALL or solid tumour<sup>17</sup>. The children were assessed at diagnosis and 1 year post-diagnosis. During the year, femoral BMD and apparent volumetric density significantly decreased in the patient group, while the age- and sex-matched controls demonstrated annual increments. Markers of bone formation (type I collagen carboxylterminal propeptide and serum osteocalcin) were significantly lower at diagnosis among the children with cancer than controls, with these results indicating that the disease process impairs skeletal status. By 1 year post-diagnosis, although the bone formation marker had normalised, the bone resorption marker was significantly increased. It was concluded that the deficient accumulation of bone mass may lead to an impaired development of PBM and thus may predispose the children to increased osteoporosis risk and skeletal fractures later in life<sup>17</sup>. These conclusions support those of others who have assessed the relationship between childhood cancers and skeletal status (BMD) via the use of BMD measurements.

The BMD of the lumbar spine, femoral neck, and total body was assessed using DXA, while single-photon absorptiometry was used to determine the BMD of the distal radius among 40 long-term survivors of childhood cancers (including solid tumours, lymphoma or acute leukaemia)<sup>8</sup>. Mean age at diagnosis was 12.7 years, and the mean age at time of assessment was 25.8 years. When compared with controls, the mean BMD for the patients was significantly reduced at the distal radius, femoral neck and total body, but not at the lumbar spine. Since the patients studied were at an age that coincided with the normal age of attainment of PBM, and that PBM is a primary determinant of BMD later in life, the risk for osteoporosis and fractures in the future was elevated.

Others who have compared the BMD of children with cancer to normative data have found similar results and drawn the same conclusions<sup>15, 156, 159, 402</sup>. Following the assessment of the BMD of the lumbar spine in 97 long-term survivors of childhood cancer (5-23 years post-diagnosis), it was found that approximately 13% and 32% of participants were characterised with a BMD SD score of below -2 and -1 to -2, respectively<sup>159</sup>. These results indicated that 45% of participants experienced below normal BMD levels. Height for age at follow-up and increasing doses of cranial

irradiation were inversely correlated with BMD SD scores. Other paediatric studies have reported similar results with 19–23% of patients recording greater than 2 SD below age-matched controls<sup>97, 138</sup>. Slightly lower rates were found in an investigation of 60 patients aged 5.5–20.1 years, who had been disease-free for 1.0–14.5 years<sup>156</sup>. It was reported that only 8% of these patients were more than 2 SD below age-matched normal BMD.

Previous studies have also assessed the risk of bone loss in adults diagnosed with cancer. Women diagnosed with breast cancer are at a considerable risk for the development of osteoporosis as a consequence of the early induced menopause that is commonly related to breast cancer treatment<sup>201, 219</sup>. The majority of these investigations have assessed the impact of tamoxifen treatment on BMD changes. Tamoxifen is an anti-oestrogen agent and since oestrogen receptors have been identified on osteoblasts, it was feared that tamoxifen would induce BMD loss. However, following extensive research, the effects of tamoxifen on bone remains controversial, with some investigations illustrating no effect, while others demonstrating a deleterious effect on bone<sup>214, 221, 255, 306</sup>.

Investigations involving BMD changes in patients treated with *L*-thyroxine have also been conducted. This thyroid hormone stimulates the remodelling of both trabecular and cortical bone, with the release of excessive amounts of the hormone being characterised by an uncoupling between bone resorption and formation, leading to reduced BMD<sup>140, 141</sup>. The resulting osteoporosis has been illustrated in hypothyroid patients taking replacement therapy, in adult hyperthyroid patients and in patients on *L*-thyroxine treatment to suppress thyroid stimulating hormone secretion for various diseases. In an investigation performed on patients who had undergone total thyroidectomy due to non-medullary thyroid carcinoma, and who were being treated with thyroid-suppressive doses of *L*-thyroxine, it was demonstrated that values of bone alkaline phosphatase and urinary excretion of hydroxyproline were elevated<sup>136</sup>. These results indicated an increased bone turnover and bone resorption. However, others have noted that therapeutic doses of thyroxine do not have a significant impact on BMD, and patients receiving sophisticated thyroxine therapy for the treatment of differentiated thyroid carcinoma are not at risk of developing osteoporosis<sup>140</sup>.

Changes in the BMC of children and adolescent females being treated with high doses of *L*-thyroxine have also been studied<sup>311</sup>. Results showed a significant reduction in the BMC of the proximal two-thirds of the forearm, but not in the distal one third. Since cortical bone is more susceptible to thyroid hormones, and the proximal site is more representative of cortical bone, the results are in accordance with the literature.

The potential for inducing bone loss in patients with cancer is further elevated when combination treatment, involving the concurrent use of radiation and chemotherapy, or the combination of several bone-influencing chemotherapeutic agents, is administered<sup>82</sup>. Treatment options such as BMT and PBST involve the use of this combination treatment and, as such, reduced BMD is a common finding in patients following BMT<sup>433</sup>.

The pre-transplant myeloablative therapy in autologous and allogenic patients has been associated with changes in biochemical markers of bone metabolism in the initial 12 weeks post-transplant and has suggested a reduction in bone formation and an elevation in resorption<sup>61</sup>. The inhibitory effect of glucocorticosteroids upon bone formation, the damage to osteoprogenitor cells by the myeloablative therapy and the inhibition of osteoblast function by locally-secreted cytokines were given as potential reasons for the shown effect. Another investigation performed on 27 women aged 16-49 years who received either an allogenic or autologous transplant assessed biochemical markers of bone formation and resorption, and evaluated the presence of osteopenia and osteoporosis by DXA<sup>64</sup>. According to the World Health Organisation criteria, 33% and 18% were diagnosed as osteopenic and osteoporotic, respectively. Osteocalcin bone Gla-protein was elevated in 6 out of 20 analysed cases, while procollagen type I carboxyterminal propeptide was increased in 10 out of 19 cases, indicating an accelerated bone formation. Bone resorption markers also indicated an accelerated bone turnover, with 95% of patients demonstrating an elevation in the hydroxyproline/creatinine ratio.

Stern and associates (1996)<sup>375</sup> investigated changes in BMD in patients with clinical extensive chronic graft-versus-host disease (GVHD), and who were receiving treatment with prednisone and cyclosporin A. The researchers followed bone

turnover and density parameters over 9-months, during the treatment for chronic GVHD. Despite an adequate dietary calcium intake, biochemical parameters revealed increased bone turnover. Urinary calcium and hydroxyproline excretion were initially elevated and remained high throughout the course of the investigation. Additionally, dual photon absorptiometry revealed that significant osteopenia of the lumbar spine had developed in six out of eight of the patients investigated. The female patients were at an elevated risk compared to males, and males who experienced greater post-transplant complications were at an increased risk when compared to those that had fewer complications.

Withold et al (1996)<sup>433</sup> measured serum bone alkaline phosphatase and urinary pyridinium cross-links in 21 bone marrow transplant patients (18 patients received an allogenic transplant, while 3 underwent an autologous transplant) approximately 281 days post-transplant. All participants recorded an elevation in the urinary excretion values of pyridinium cross-links, while only the female subjects displayed significantly higher serum bone alkaline phosphatase values when compared with age- and sex-adjusted controls. The increase in bone formation for the females potentially reflected primary ovarian failure and an enhancement of bone resorption, possibly mediated by circulating interleukin-6.

Another investigation performed on allogenic BMT patients, not only studied bone loss and turnover following transplant, but also assessed whether bone loss could be prevented by administration of calcium with or without calcitonin<sup>398</sup>. Dual energy X-ray absorptiometry was used to assess BMD, while several biochemical markers were employed to assess bone turnover. Calcium with or without calcitonin had no effect on bone loss or bone markers, and BMD reduced in the lumbar spine and femoral sites. Markers of bone formation reduced during the initial weeks, but then returned to baseline by 6 months. This was in conjunction with elevations in the bone resorption marker (serum type I collagen carboxyterminal telopeptide) which stayed above normal throughout the entire observation period. At the end of the study, 58% of patients had osteopenia at least in the femoral neck. However it is important to note that the majority of the patients were experiencing a reduced bone mass even at the beginning of the study.

A change in bone mass of one SD (of the normal population) elevates fracture risk by an estimated 100%<sup>218</sup>. Additionally, a reduction in femoral neck BMD by one SD from the age-adjusted mean has been shown to increase the risk of hip fracture by a factor of 2.6 in women over the age of 65 years<sup>83</sup>. These data highlight the significance of findings demonstrating adverse changes in bone turnover and bone mineral density.

Not all investigations regarding the effect of BMT on skeletal status have found adverse results. Keilholz and colleagues (1997)<sup>193</sup> investigated the endocrine function and bone metabolism of 29 patients who had successfully undergone an autologous BMT or PBST and did not show any significant late effects on these factors. Others have assessed BMD changes in patients with multiple myeloma treated either by conventional chemotherapy or high-dose chemotherapy and/or radiotherapy, followed by autologous PBST<sup>233</sup>. Following treatment, a 4.1% and 3.9% increase in lumbar BMD was demonstrated in patients with a partial or complete response, and patients with refractory disease, respectively. These results were consistent with a previous investigation performed by the same investigators on a similar population, which demonstrated that lumbar BMD increased by approximately 8% in males, but did not show any change in females<sup>234</sup>. However, in comparison with the elevation in lumbar BMD, total body BMD data decreased and were related to a reduction of the appendicular BMD.

In summary, substantial evidence associates cancer and oncology treatment with an adverse effect on skeletal status. Furthermore, an inadequate diet and/or extensive periods of hospitalisation and bed rest can also contribute to the elevated risk of bone loss in patients with cancer.

#### **7.1.2.2 Dietary-related bone loss**

Dietary-related bone loss may be caused by chronic dietary deficiencies of calcium, protein, vitamin D, which regulates calcium deposition, and/or vitamin C, which is an essential cofactor in collagen metabolism<sup>189</sup>. Therefore any condition or disease process which influences total food intake or the ability to digest food and absorb nutrients has the potential to influence bone turnover.

Certain types of cancer, such as gastrointestinal cancer, will influence the ability to digest and absorb food<sup>420</sup>, while certain treatment regimens induce side effects that will influence total dietary intake. Many chemotherapeutic agents, including dactinomycin, bleomycin, cyclophosphamide, 5-fluorouracil, methotrexate and vincristine, can lead to side effects including constipation, nausea, vomiting, diarrhoea, dry mouth and mouth sores, which in turn reduce food intake<sup>67</sup>. Patients who have received high-dose chemotherapy and/or radiotherapy, such as PBST patients, are at a particularly high risk of experiencing these symptoms<sup>68</sup>.

However, research demonstrates that bone loss may be unavoidable even in the presence of an adequate diet. An investigation performed on allogenic BMT patients experiencing chronic GVHD found that despite an adequate diet intake, biochemical parameters still revealed an increased bone turnover<sup>375</sup>. A more recent investigation also performed on allogenic BMT patients demonstrated supportive findings<sup>398</sup>. Bone loss experienced by these patients could not be prevented by administration of calcium with or without calcitonin. Therefore, while an inadequate diet is a potential contributing factor to bone loss, an adequate diet may be unable to prevent bone loss in patients with cancer. Consequently, other bone loss prevention strategies need to be investigated.

### 7.1.2.3 Disuse-related bone loss

Reduced levels of physical activity or bed rest are additional contributing factors for bone loss. Prolonged periods of disease and treatment are related to hospitalisation, and hospitalisation periods are associated with reduced levels of physical activity<sup>17</sup>.

Osteoporosis caused predominantly by disuse occurs as a consequence of alterations in bone mass in response to the changing environmental stimuli. In order to match the mechanical demands applied to bone, bone maintains the ability to remodel by altering its size, shape and structure<sup>269</sup>. Wolff's Law (1892), "bone is laid down where needed and resorbed where not needed", summarises the phenomenon in which cancellous and/or cortical bone is gained or lost as a consequence of the demands applied<sup>269</sup>. Later investigations regarding the effects of physical activity or

disuse have continually substantiated this theory, which was proposed over 100 years ago.

### **Reduction in physical activity and associated bone loss**

Evidence exists from as early as 1921 that immobilisation, disuse, bed rest and weightlessness can elicit deleterious effects on bone structures<sup>167, 253</sup>. If, due to partial or total immobilisation, bone does not undergo the usual mechanical stresses, then periosteal and subperiosteal bone is resorbed with a consequent reduction in strength and stiffness and increase in risk of osteoporosis<sup>269</sup>. Additionally, it has been reported that neither endocrine nor dietary intervention can compensate for bone loss associated with inactivity<sup>239</sup>.

Research investigating the relationship between immobilisation and bone remodelling has been undertaken by studying animals, patients with casted limbs, amputees and space flight subjects. These studies suggest that following immobilisation periods as short as 2 weeks, systemic and local changes may influence BMD<sup>153, 176, 312, 441</sup>. An increased number of osteoclasts, an increased bone resorption activity, and a decreased rate of bone formation have been observed morphologically after both short-term and long-term bed rest<sup>19</sup>. However, the ratio between calcified and noncalcified matrix, as well as the chemical composition of bone, remain essentially unchanged<sup>186</sup>.

Biochemical markers of bone turnover display rapid alterations following bed rest with urinary markers of bone resorption such as the hydroxyproline/creatinine, calcium/creatinine, and deoxypyridinoline/creatinine ratios increasing within the first week<sup>399</sup>. Similarly, serum markers of bone resorption such as tartrate-resistant acid phosphatase and cross-linked carboxyl-terminal telopeptide of collagen type I also increase a few days after commencing bed rest. The carboxyl-terminal propeptide of type I procollagen (PICP), which reflects the synthesis of type I collagen, has been shown to gradually reduce after bed rest commences<sup>285</sup>. Simultaneously, the level of urinary deoxypyridinoline/creatinine (uDPyr/Cr) has been shown to increase. It was therefore suggested that by using uDPyr/Cr and PICP as biochemical markers of bone turnover, there is an apparent uncoupling of bone resorption and formation

within the first few days of bed rest<sup>285</sup>. Studies of premenopausal women have shown that serum osteocalcin and serum alkaline phosphatase decreases and uDPyr/Cr increases with immobilisation<sup>285</sup>.

Since osteocalcin is a direct product of osteoblasts and is known to reflect the activity of the mineralisation phase of the newly-formed bone matrix, osteocalcin has been used to investigate the impact of immobilisation on bone<sup>185</sup>. Following the immobilisation of rats for three weeks, the immunoreactivity of osteocalcin was markedly decreased or was completely absent in all the patella areas studied. Normally these areas show intense reaction as a sign of mineralisation of the newly-formed bone.

LeBlanc and colleagues (1995)<sup>208</sup> showed in their investigation on males that urine and faecal calcium increase and a negative calcium balance arises with bed rest. A reduction in true calcium absorption of 22% from baseline, and a 17% decrease in vitamin D accompany these changes. Additionally, the cross-links pyridinium and deoxypyridinium were elevated (32–37% above baseline) during bed rest, indicating that resorption was increased. However, it was further suggested that bone loss was related to an increase in bone resorption rather than a decrease in bone formation. The maintenance of alkaline phosphatase and osteocalcin levels during the bed rest period indicated that bone formation did not decrease<sup>208</sup>.

Furthermore, studies that have assessed the effect of weightlessness on humans during space travel have demonstrated detrimental changes in bone turnover. A negative calcium balance, an increase in urinary and faecal calcium excretion, and loss of calcium and phosphorus have been shown following periods of weightlessness<sup>92, 380, 382</sup>.

Studies assessing changes in BMC and BMD with bed rest or immobilisation have reported similar findings to those investigations assessing changes in biochemical markers. An immobilisation study on growing chicks caused a reduced gain in bone mass and length, reduced bone curvature and, in some cases, reversed bone curvature<sup>32</sup>. The 14% reduction in bone length found in the immobilised chicks was similar to that observed for children with congenitally paralysed limbs<sup>32</sup>.

A 29% reduction in the trabecular volume of sheep's hind legs was observed following a 12-week immobilisation period<sup>387</sup>. Similar findings were also found in an investigation assessing both immobilisation and partial immobilisation on sheep calcaneus<sup>365</sup>. Partial immobilisation was classified as immobilisation of the calcaneus with periods of remobilisation set at 'normal' walking speeds for 20 minutes/day. It was identified that the BMC of both the total and partial immobilisation group, was significantly reduced by 22% and 21%, respectively. The significant loss in the partially-immobilised group seemed unusual, since by definition it is the bone's normal strain environment which prevents disuse-associated bone loss<sup>365</sup>. However, it was previously hypothesised that the main osteoregulatory stimulus to the skeleton is derived from unusual strains engendered by the inevitable loading 'accidents', and not from the normal strains of controlled functional activity<sup>202</sup>.

Finally, space flight investigations have also shown detriments in BMC and BMD. Rats subjected to periods of weightlessness have shown that cortical and trabecular bone mass, mineral content, osteocalcin production, periosteal bone formation, growth hormone secretion, bone growth turnover and vertebral apatite crystal size/perfection are significantly reduced<sup>442</sup>. Humeral flexural rigidity, elastic modulus, load at the proportional limit, tensile stress and maximum load were all significantly greater in control rats than in spaceflight rats.

The evidence demonstrating the relationship between reductions in weight-bearing physical activity and an elevated risk of bone loss is compelling. Unfortunately, cancer patients are at risk of experiencing significant reductions in physical activity following diagnosis and treatment. An observational design investigation classified patients with cancer as having 'low' levels of physical activity and found that 24% of BMT patients failed to perform any activity throughout the day, including walking, during periods of hospitalisation<sup>80</sup>. Of those who were considered 'active', the mean duration of walking and stationary cycling fell short of 8 minutes per day. Additionally, children who had received treatment for acute lymphoblastic leukaemia maintained low participation rates in physical activity, when compared with age- and sex-matched controls<sup>411</sup>.

### **Physical activity and associated bone gain**

Just as declines in weight-bearing physical activity have been associated with bone loss, loading has been related to bone gain. Weight-bearing athletes have a greater BMD when compared with the 'general population'<sup>268</sup>, and 'physically active' children have a significantly higher BMD when compared with 'less physically active' children<sup>366</sup>. Additionally, young army recruits have demonstrated increases in BMD following a 3-month weight-bearing physical activity intervention program<sup>232</sup>, while the majority of studies implementing physical activity as an intervention for osteoporosis have shown a reduction in the rate of bone loss in elderly patients<sup>87</sup>. Studies demonstrating a 35% greater bone mass in the dominant arm of tennis players compared with the non-dominant arm<sup>182</sup> and runners illustrating an elevation in bone mass in the calcaneus<sup>421</sup>, highlight that the effect of exercise on bone mass, is site-specific.

Benefits to BMD are not just derived from participation in weight-bearing physical activity, as studies assessing the influence of resistance training on BMD have also shown positive results. Improvements in femoral neck BMD following a heavy resistance training program in older men has been previously reported<sup>330</sup>. A more recent investigation regarding resistive training and BMD has shown that strength training maintains BMD in conjunction with improving muscular strength in postmenopausal women. The ability to improve muscular strength in conjunction with maintaining BMD has the potential to reduce the incidence of falls and thus osteoporotic fractures<sup>329</sup>.

The evidence relating participation in weight-bearing physical activity and resistance training with bone gain provides hope for the role of physical activity as an intervention for patients at risk of bone loss. However, periods of bone loss associated with disuse are divided into phases, and the ability of any intervention to influence bone loss may ultimately depend upon the phase at which the intervention was initiated.

### 7.1.3 Phases of bone loss

Disuse osteoporosis has been described as comprising an active and inactive phase, with the active phase consisting of an initial period of rapid loss, a recovery period, and finally a period of slower more lasting bone loss<sup>395</sup>. Following the initial period of bone loss, which tends to reach a maximum at the end of 6 weeks, bone mass may then improve. The inversion of the bone balance following the phase of rapid loss has been explained by the osteoblastic response to the relatively increased strain exerted on thinner and/or less trabecular bone<sup>387</sup>. The final period of the active phase of bone loss, is characterised by a stabilisation in bone mass at values 30-50% below the initial value. During this latter phase, the absence of mechanical force results in diminished bone formation and leaves the bone resorption activity temporarily unopposed. While the exact extent of both processes is yet to be fully determined, it was estimated that approximately 30% of total immobilisation-induced bone loss in experimental rats is caused by increased bone resorption, and about 70% by reduced bone formation<sup>185</sup>.

A steady state is reached when bone formation restores equilibrium of resorption, most likely after the first 5-6 months. The inactive phase of disuse osteoporosis starts at approximately this time. It is during this stage that bone loss nadir and less bone mass is maintained<sup>45, 167</sup>. Research indicates that reversal of bone loss is dependent on the time of remobilisation. That is, whether mobilisation is established in the active phase, prior to the establishment of long-term bone loss. Factors including age and the particular bone involved will also influence the ability to recover lost bone<sup>419</sup>.

### 7.1.4 Remobilisation

Reconstruction of bone is a much slower process than its resorption<sup>167</sup>. It was identified that the first radiographic signs of bone organisation did not appear until three to four weeks after plaster immobilisation in rabbits, whereas bone resorption was evident at the end of the second week of immobilisation. A period of 8 weeks free remobilisation following a period of 3 weeks immobilisation is not sufficient to return the patellar expression of osteocalcin in rats to normal<sup>185</sup>.

The greatest recovery in bone mass in immobilised dog limbs occurred when remobilisation was initiated during the active phase of disuse osteoporosis<sup>176</sup>. Further, long-term immobilisation could lead to losses in bone mass that may never be recovered. Even following 5 years of remobilisation, the os calcis BMC of the nine crew members of a Skylab experiment remained lower than preflight values<sup>389</sup>. Another investigation demonstrated that BMD values of a previously immobilised limb (cast-treated tibial shaft fracture) were 4-11% lower than those in the contralateral limb, even after 10 years of remobilisation<sup>186</sup>.

While the potential for recovery of an immobilised bone is a controversial issue, it seems that recovery is possible if the remobilisation and follow-up time are long enough, and if the immobilisation period has not exceeded 5-6 months – the time limit between the active and inactive phases of immobilisation induced osteopenia. What is certain is that time needed for recovery is longer than the time needed to produce osteopenic changes<sup>186</sup>.

In summary, much data have been presented that highlight the elevated risk and presence of bone loss in patients with cancer. The roles of weight-bearing exercise and strength training in preventing or reversing bone loss have also been previously proven in numerous populations. However, limited data exist to describe the importance of remobilisation during and/or following cancer treatment, for improved long-term skeletal status. Only one investigation could be identified that assessed the relationship between physical activity levels and skeletal status. Higher levels of physical activity were associated with improved BMC in children with acute lymphoblastic leukaemia<sup>412</sup>. Although information is limited, it has been recently recommended that patients with cancer should resume weight-bearing exercise as soon as possible in order to avoid or reduce bone loss<sup>398</sup>. However, more research is required within the area to determine the influence of physical activity in preventing bone loss, reducing the rate of bone loss, or reversing bone loss associated with cancer patients.

## 7.2 Methodology

Chapter 3 provides a detailed outline of the methodological procedures relating to subject recruitment, the testing phases and the intervention program implemented. In summary, 12 patients, with 6 patients in each group were recruited. Of these, only 7 patients were recruited at PI, while the remaining subjects entered the investigation at PII. Outlined below are the methodological procedures which relate specifically to the aims of this section of the investigation and involve the biochemical assessment of two markers of bone turnover, urinary hydroxyproline and serum alkaline phosphatase.

### 7.2.1 Biochemical markers of bone turnover

As previously discussed, a number of biochemical markers are used to routinely determine bone turnover. The markers used in this experiment were selected on the basis of the value of the information to be derived from the marker, cost, and ease of implementation. While the markers chosen (serum alkaline phosphatase and urinary hydroxyproline) are not specific indicators of bone metabolism, they have previously been used to provide information in bone metabolism research and in clinical situations<sup>321</sup>. For example, the measurement of urinary hydroxyproline values, together with alkaline phosphatase, has proven useful in detecting accelerated bone loss in postmenopausal women<sup>112</sup>.

Qualified laboratory technicians in Queensland Medical Laboratories performed the assessment of both markers, and a summary of the experimental procedures implemented is outlined below.

### 7.2.2 Marker of bone resorption – urinary hydroxyproline/creatinine

Measurement of urinary hydroxyproline, corrected for creatinine, has provided information with regards to bone catabolism. The concentration of hydroxyproline in the urine corresponds to the collagen content in tissue and is therefore a good indicator of collagen metabolism. Since half of human collagen resides in bone,

where its turnover is potentially faster than in soft tissues, hydroxyproline excretion in urine is regarded as an effective marker of bone resorption<sup>93</sup>. During bone turnover, there is also an increased release of hydroxyproline from the bone matrix, which is excreted by the kidney and subsequently, urinary hydroxyproline levels increase.

A 24-hour urine sample was collected in an acid-preserved (25ml of 6M hydrochloric acid) container for the assessment of urinary hydroxyproline (uHP). An accurate 24-hour collection is essential for uHP determination, as there is diurnal rhythm of excretion, which is maximal between midnight and 8.00 am<sup>434</sup>. Dietary collagen is catabolised and, in part, excreted as hydroxyproline peptides. Therefore, patients were instructed to follow a low-collagen diet during the 24-hour collection period and for the 24-hours prior to collection. Meat, fish, meat extracts and all gelatine-containing foods such as jellies, canned foods, processed meat, chocolates, ice-cream and cream biscuits were avoided.

Bound hydroxyproline present in the 24-hour sample was converted into free form by acid hydrolysis, and resin and charcoal were used to remove any contaminants<sup>434</sup>. The neutralised hydrolysate was oxidised with chloramine-T and decarboxylated to produce a pyrrole – which then reacted with Ehrlich's reagent and was detected spectrophotometrically at 560nm. Most methods rely on hydrolysis and oxidation of hydroxyproline and subsequent colour production. Standards are also used to limit interference by similarly reacting compounds. In summary, the steps implemented to obtain results included hydrolysis, preparation of fresh reagents, removal of interfering compounds, neutralisation, oxidation, colour reaction and finally, absorbance was read<sup>434</sup>. The uHP result was reported to the nearest 5  $\mu\text{mol}/24\text{hr}$  and was then adjusted for urinary creatinine according to the formula:

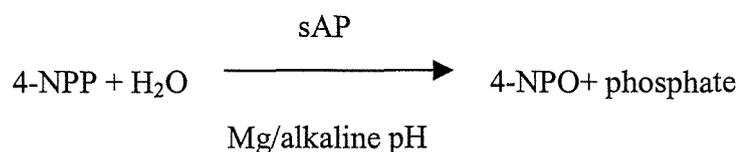
$$\text{uHP/Creatinine Ratio} = \frac{\text{uHP } (\mu\text{mol}/24 \text{ h})}{\text{Urinary Creatinine } (\text{mmol}/24\text{h})}$$

The uHP/creatinine (uHP/Cr) ratio was reported to the nearest whole number in  $\mu\text{mol}/\text{mmol}$ .

### 7.2.3 Marker of bone formation – serum alkaline phosphatase

Total alkaline phosphatase has been correlated with osteoblast activity and is used to provide a measure of bone formation<sup>378</sup>. Determination of total activity provides critical information for bone turnover, however differentiation between sources (tissue-nonspecific including bone, liver, kidneys, intestinal and placental) is not possible<sup>310</sup>. Additionally, substances such as bilirubin, phosphate, bile acids, urea, glucose and certain drugs can interfere with these measurements. While these factors are known limitations to the measurement of bone formation activity, previous findings<sup>296</sup> have failed to demonstrate a clear superiority of bone-specific versus total alkaline phosphatase measurement.

The assessment of serum alkaline phosphatase (sAP) required the collection of 10ml of blood in a heparin tube, which was then stored at room temperature until it reached the pathology testing laboratories. The methodology used to measure sAP was based on the recommendations of the International Federation of Clinical Chemistry, and utilised 4-nitrophenylphosphate (4-NPP) as the substrate and 2-amino-2-methyl-1-propanol as the buffer<sup>310</sup>. Under the optimised conditions, sAP present in the sample catalysed the following transphosphorylation reaction:



At the pH of the reaction, 4-nitrophenoxide (4-NPO) has an intense yellow colour. The reagent also contains a metal ion buffer system to ensure that optimal concentrations of zinc and magnesium are maintained. The metal ion buffer also chelates other potentially inhibitory ions which may be present. The reaction was monitored by measuring the rate of increase in absorbance (Abs) at 405nm which is proportional to the activity of sAP in the serum.

A clinical chemistry analyser (Technicon Dax System, Bayer) capable of maintaining constant temperature (37°C) was used to measure sAP activity in units per litre (U/L):

$$\text{Activity in U/L} = \Delta\text{Abs/min} \times \text{Factor},$$

$$\text{Factor} = \frac{TV \times 1000}{18.8 \times SV \times P}$$

where

*TV* = total reaction volume in ml

*SV* = sample volume in ml

18.8 = millimolar absorption coefficient of  
4-nitrophenol at 405nm

*P* = cuvette pathlength in cm

Circadian rhythms can be observed in nearly all markers of bone metabolism and can range from 10-15%<sup>378</sup>. The time of testing was therefore standardised for all patients, with blood tests being performed between 8.00am and 10.00am, and the urine sample was commenced on awakening and continued until the same time the following morning.

#### 7.2.4 Statistical Analysis

Bone turnover data were collected at each of the three testing phases and were analysed according to the statistical procedures outlined in Chapter 3. Additionally, the relationship between bone formation and resorption activity was assessed for the SG at PI and PII, and the CG and EG at PIII via the use of a Pearson correlation.

### 7.3 Results

Changes in bone resorption and formation following the transplant are presented in Table 7.2. Pre-transplant, the range for uHP/Cr and sAP was 12-40  $\mu\text{mol}/\text{mmol}$  and 56-115 U/L, respectively. The mean for the bone resorption marker was outside the normal range at PI, while the mean formation marker was well within the usual range. All individual values for sAP levels at PI were within the normal range. Following the PBST, the rate of bone turnover increased, with a significant change ( $p < 0.05$ ) being detected in the bone resorption marker (range at PII = 8–60  $\mu\text{mol}/\text{mmol}$ ). In addition, only 33% of patients at PII recorded uHP/Cr levels within the normal range. Mean bone formation also increased (range = 48–185 U/L), however, only 25% of patients recorded sAP levels outside the normal age- and sex-matched range.

**Table 7.2** Bone turnover measures at PI and PII for the study group (mean $\pm$ SE)

SG		PI n = 7		PII n = 12		p value
Bone turnover marker	NR	Mean	SE	Mean	SE	
uHP/Cr ( $\mu\text{mol}/\text{mmol}$ )	5-25	25.42	2.50	33.58	1.80	0.018*
sAP (U/L)	30-115	80.88	13.07	92.50	9.38	0.482

NR = Age- and sex-matched normal range

\*  $p < 0.05$

The change in bone turnover across the testing phases for the control group is presented in Table 7.3. While no significant differences were observed in markers across the phases, the mean change demonstrated a trend towards an elevation in bone turnover following the transplant, and a reduction in bone turnover during the recovery period. Undertaking a PBST led to an elevation in bone resorption, shifting uHP/Cr levels to outside the normal range. By 3-months post-transplant, levels had returned to just within the normal range (5–25) but remained above pre-transplant levels. At PIII, 40% of patients were still recording uHP/Cr levels outside the normal range, with an additional patient recording uHP/Cr levels at 25  $\mu\text{mol}/\text{mmol}$ . Mean bone formation was within the normal range for all three phases, with only 2

patients at PII recording individual levels above the range. However, a mean increase in sAP was observed by PII, with a corresponding reduction in activity by PIII. Three-months post-transplant, bone formation was lower than PI levels, in contrast to the higher mean bone resorption activity at PIII, when compared with PI.

**Table 7.3** Bone turnover measures across the testing phases for the control group (mean $\pm$ SE)

Bone turnover marker	Phase	n	Mean	SE	Comparisons	p value
uHP/Cr ( $\mu$ mol/mmol)	I	3	23.29	4.08	PI-PII	0.172
	II	6	30.50	2.54	PII-PIII	0.186
	III	5	24.92	2.92	PI-PIII	0.757
sAP (U/L)	I	3	78.22	21.31	PI-PII	0.536
	II	6	96.50	13.27	PII-PIII	0.349
	III	5	73.73	15.22	PI-PIII	0.887

Table 7.4 demonstrates the change in bone turnover across the testing phases for the exercise group. The mean uHP/Cr activity levels at pre-treatment were outside the normal range and demonstrated a further significant increase by PII. At conclusion of the exercise intervention, levels at PIII had fallen significantly to within the normal range. The range varied at each phase and was recorded at 12-40  $\mu$ mol/mmol, 20-60  $\mu$ mol/mmol and 13-34  $\mu$ mol/mmol, at PI, PII and PIII, respectively. Serum alkaline phosphatase was elevated as a result of the transplant, and remained higher than pre-transplant and similar to PII levels, at PIII. Across the testing phases only 1 patient at PII, and 1 patient at PIII, recorded sAP levels outside the normal range (145 and 120, respectively).

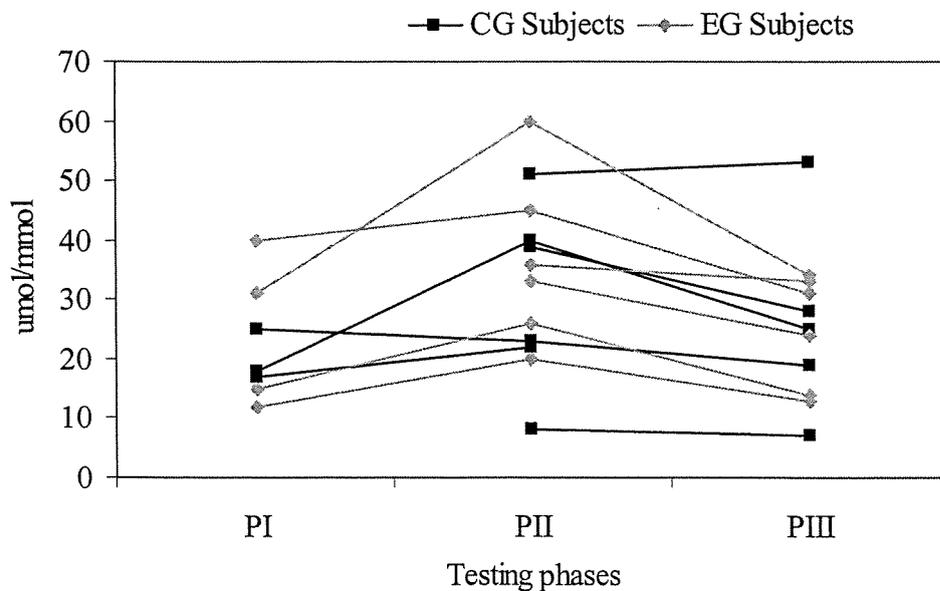
**Table 7.4** Bone turnover measures across the testing phases for the exercise group (mean±SE)

Bone turnover marker	Phase	n	Mean	SE	Comparisons	p value
uHP/Cr (µmol/mmol)	I	4	27.55	2.90	PI-PII	0.046*
	II	6	36.67	2.54	PII-PIII	0.010*
	III	6	24.83	2.54	PI-PIII	0.508
sAP (U/L)	I	4	83.54	15.15	PI-PII	0.793
	II	6	88.50	13.27	PII-PIII	0.983
	III	5	88.10	15.15	PI-PIII	0.823

\* p<0.05

With respect to bone apposition, there were few variations in individual changes, in contrast to the marked intra-group differences in bone resorption (Figure 7.1). The subjects in the exercise group demonstrated the same trend of change between each of the testing phases. While the majority of subjects in the control group demonstrated a slight reduction in resorption activity post-transplant, one subject displayed an increase in activity.

**Figure 7.1** Individual changes in urinary hydroxyproline/creatinine across the phases for the subjects in the control and exercise group



Following a PBST, a significant positive correlation between bone resorption and bone formation activity was found (Table 7.5). By 3-months post-transplant, a positive relationship between the biochemical markers of bone turnover remained evident in the control group subjects, however, the reduction in data points reduced power and therefore the ability to detect significant differences. In contrast, by PIII, no relationship between the markers was identified for the EG.

**Table 7.5** Correlations of the bone turnover measures

Group	Phase	Relationship between uHP/Cr and sAP	
SG	PI	Pearson Correlation	-0.198
		Sig. (2-tailed)	0.639
		n	7
SG	PII	Pearson Correlation	0.611*
		Sig. (2-tailed)	0.035
		n	12
CG	PIII	Pearson Correlation	0.485
		Sig. (2-tailed)	0.407
		n	5
EG	PIII	Pearson Correlation	-0.023
		Sig. (2-tailed)	0.971
		n	6

\*  $p < 0.05$ , \*\*  $p < 0.01$

## 7.4 Discussion

Biochemical markers used to assess bone turnover demonstrated that bone resorption was elevated pre-PBST and continued to increase post-transplant, as was indicated by the significant change in uHP/Cr between PI and PII. A PBST was also associated with an elevation in bone formation, however the mean change was not significant. Bone resorption significantly reduced to mean levels that were lower than that recorded at pre-transplant, following participation in the 3-month aerobic and resistance training program. Additionally, by PIII, mean bone formation of the exercising patients was higher than pre-transplant values. In contrast, the non-exercising patients demonstrated a mean reduction in bone formation to below pre-transplant levels within 3-months post-transplant. However, the changes observed in the bone formation marker were not significant for either the exercising or control group.

### 7.4.1 Impact of the transplant on bone turnover

Bone resorption increased by 32% following the transplant and reached activity levels outside the normative range. The average increase for bone formation was 14%, but this was not a significant change. Therefore, while bone turnover is elevated immediately post-transplant, the results suggest an uncoupling of bone resorption and formation, favouring resorption. A similar trend towards an elevation in bone turnover, where both resorption and formation elevate, with the former exceeding the latter, has been reported following loss of ovarian function<sup>230</sup>. Additionally, the significant change detected in the uHP/Cr ratio between PI and PII of this study supports previous findings which have demonstrated that with bed rest, urinary markers of bone resorption such as uHP/Cr, calcium/creatinine and deoxypyridinoline/creatinine ratios can increase within the first week<sup>19, 399</sup>. Additionally, the results of this investigation are similar to earlier findings which have shown an elevation in urinary calcium and uHP excretion following allogenic transplant<sup>375</sup>, and an elevation in the uHP/Cr ratio following either an allogenic or autologous transplant<sup>64</sup>.

The significant change in bone resorption detected between the pre- and post-transplant phases could be explained by the influence of certain chemotherapeutic drugs, such as glucocorticoids and methotrexate, on bone turnover. Glucocorticoids appear to be the primary cause of the uncoupling of reduced bone formation and increased resorption<sup>398</sup>, while methotrexate influences bone turnover by increasing bone resorption<sup>188</sup>.

In addition to the treatment effect on bone resorption, is the influence of a reduction in physical activity levels during the treatment period. The PBST transplant process induces a period of hospitalisation lasting approximately 1-week. Additionally, 92% of the study sample were readmitted for a period that ranged between 1-3 weeks, following the transplant due to the presence of certain side effects. The hospitalisation period was further lengthened (approximately 12 weeks) for those patients who were required to undertake 3 consecutive PBST (n=3). The response of bone to immobilisation or bed rest has been well documented, and is devoid of normal mechanical stresses, bone strength and stiffness are reduced<sup>269</sup>. Following long-term and short-term bed rest, an elevation in the number of osteoclasts, an increased bone resorption activity, and a reduction in bone formation rate have been morphologically observed<sup>19</sup>. Therefore, it can be suggested that both the treatment administered and the period of bed rest experienced, were contributing factors to the elevation in bone resorption observed.

Finally, results from the administration of a food frequency questionnaire (details are provided in Chapter 4) demonstrated that pre-transplant, 89% of the subject population were ingesting at least 1 serving of dairy products daily, with only 11% consuming 2 or more servings per day. Therefore, at pre-transplant, the majority of patients were consuming less than the minimum daily recommendation for dairy product consumption<sup>189</sup>. However, following the transplant, the intake of dairy products further declined, with only 33% of the subjects consuming 1-2 servings per day and 58% of the subjects failing to consume at least 1 serving daily. When calcium intake is below the recommended levels, the body draws on the calcium reserves in the bone to replace the deficit<sup>189</sup>. Therefore, given that dairy products provide one of the highest sources of calcium<sup>189</sup>, the decline observed in dairy

product consumption in this investigation, is another potential contributing factor for the elevation in bone turnover and bone resorption measured.

Changes in the bone formation marker post-treatment during this investigation support previous work that has reported either no change or an elevation in bone formation markers during periods of bed rest or treatment. While there was little change in the bone formation markers, sAP and osteocalcin, during a 4-month bed rest period<sup>208</sup>, elevated levels of bone alkaline phosphatase have been shown in patients being treated for non-medullary thyroid carcinoma, with thyroid suppressive doses of *L*-thyroxine<sup>136</sup>. Two other investigations involving allogenic and autologous transplant patients have demonstrated an elevation in serum bone alkaline phosphatase 281 days post-transplant<sup>433</sup> and an increase in osteocalcin bone Gla-protein, 7-158 months post-transplant<sup>64</sup>. The elevation in the bone formation markers observed in the above investigations were attributed to an increase in bone turnover, and were also associated with increases in the bone resorption markers measured.

The attainment of PBM, the maintenance of PBM during the ages of 20-50 years, and the rate of bone loss are critical factors in the prevention of osteoporosis<sup>82</sup>. Regardless of the patient's age, undertaking a PBST may induce adverse effects on bone turnover including an inability to attain PBM, the initiation of bone loss at an early age, and an accelerated rate of bone loss. Determining intervention strategies to reverse these detrimental effects is crucial in minimising the risk of the osteoporosis in later life.

#### **7.4.2 The effect of the intervention program on bone turnover**

Participation in weight-bearing physical activity and resistance training has previously been shown to induce positive changes in bone turnover and BMD. Remobilisation following periods of hospitalisation or bed rest is also critical for reversing any bone loss. While the effectiveness of activity has been evaluated in a number of population groups including postmenopausal and elderly groups<sup>87, 329, 330</sup>, this is the first investigation that has assessed the importance of activity for skeletal health in cancer patients. The results of this investigation demonstrated that

participation in the aerobic and strength training program following a PBST was associated with beneficial changes in bone turnover, in particular bone resorption. Following the exercise intervention period, the EG demonstrated a significant decline (33%) in the mean bone resorption activity, with all exercising patients displaying a reduction in bone resorption activity, in conjunction with a marginal mean decline of 0.5% for bone formation. These results indicated that an uncoupling of bone resorption and formation existed during the intervention period for the exercising patients, with the uncoupling favouring formation.

While both bone resorption and bone formation markers decreased for the control group during the intervention period, mean uHP/Cr was higher, while mean sAP was lower, at PIII when compared with pre-treatment levels. However, the differences between the PI and PIII marker activities, were not significant. It could be suggested that although the bone turnover markers followed the same trend post-transplant, bone turnover activity for the CG, may have favoured resorption. That is, greater increments were observed in uHP/Cr between PI and PII and lower decrements between PII and PIII, when compared with the formation marker.

Following the 3-month intervention period, the CG and EG recorded similar mean uHP/Cr levels (24.92 and 24.83umol/mmol, respectively). However, the exercising participants demonstrated higher mean sAP levels (88.1U/L) when compared with the non-exercising subjects (73.73U/L). Although these differences were not significant, the change in the markers suggests that participation in an aerobic and resistance training program, has the potential to reduce the rate of bone resorption, while maintaining or increasing the rate of bone formation. In turn, the beneficial effects on bone turnover following the transplant could potentially lead to an improved skeletal status in the future, and a reduction in the risk of osteoporosis.

Differences in the direction of the relationship of the bone turnover markers measured in this investigation were observed. Prior to the transplant, no relationship was detected between bone resorption and formation activity. However, following the transplant, a significant positive relationship between the 2 bone turnover markers was identified, whereby the higher the resorption activity, the higher the formation activity. This positive relationship was maintained by the CG up to 3-

months post-transplant, however the reduction in data points at PIII reduced statistical power, and therefore the results were not found to be significant. In contrast, undertaking the aerobic and resistance training program was associated with a change in the relationship of the two markers, so that again, no relationship was identified between the formation and resorption activity. These results indicate that formation activity was maintained while resorption activity reduced, in the exercising patients

It should however be noted that inconsistencies also exist throughout the literature regarding the relationship between bone formation and resorption markers. While significant correlations between resorption and formation markers have been reported in primary<sup>345</sup> or secondary hyperparathyroidism<sup>431</sup>, bone metastases<sup>432</sup>, and in patients with breast cancer-induced osteolysis<sup>46</sup>, previous work in patients with cancer following BMT has found that the resorption and formation activity are unrelated<sup>433</sup>.

Regardless of whether the patients in this investigation were exercising or control participants, the uHP/Cr levels returned to within the normal range by 3-months post-transplant. These results are in contrast to earlier investigations of bone turnover following BMT. Elevated levels of uHP for a period of 9-months post-transplant have been shown in patients who had undergone an allogenic transplant<sup>375</sup>. However, the patients were receiving treatment for extensive GVHD throughout the 9-month period, which may explain the continued elevation in bone resorption. Nevertheless, an investigation following patients for a 12-week period post-autologous or allogenic-transplant also demonstrated an elevation in bone resorption, in conjunction with a reduction in bone formation activity. The inhibitory effect of glucocorticosteroids upon bone formation, the damage to osteoprogenitor cells by the myeloablative therapy, and the inhibition of osteoblast function by locally secreted cytokines were given as potential reasons for the elevated resorption.

It is possible that the differences between the calcium intake of the control and exercise groups following the transplant may have contributed to the changes observed in bone turnover in this investigation. Results from the food-frequency questionnaire demonstrated that 40% of the control group, compared with only 17%

of the exercising group, did not consume dairy products daily. However, findings from previous analyses regarding the role of calcium intake in preventing or reversing bone loss following a BMT, suggest otherwise. An investigation on allogenic transplant patients found that, despite an adequate calcium intake, an elevation in bone turnover continued post-transplant<sup>375</sup>. Further, calcium intake, with or without calcitonin, had no influence on bone loss in a more recent investigation utilising allogenic transplant patients<sup>398</sup>. It therefore seems likely that dietary interventions have limited effect on bone turnover and BMD during or following a BMT.

Finally, although preliminary and limited by subject numbers, the changes detected in the biochemical markers should not be underestimated. Future research including longer intervention periods, greater subject numbers and the inclusion of BMD measurement, will be important to confirm the findings of this investigation and to determine their clinical and long-term significance.

## **7.5 Conclusion**

In summary, bone resorption was significantly elevated following the transplant, indicating that autologous PBST patients are at risk of bone loss during and after the treatment period. It is crucial for long-term skeletal integrity and health that the bone turnover and BMD of these patients be monitored following a transplant. It is also important to implement intervention strategies that will work towards preventing, minimising and/or reversing the bone loss experienced by patients with cancer. Physical activity is one such potential intervention strategy. The exercising PBST patients demonstrated that regular participation in weight-bearing exercise and resistance training led to a significant decrease in bone resorption activity, in conjunction with the maintenance of higher than pre-transplant bone formation activity. This is in contrast to the mean decrease in both resorption and formation activity by 3-months post-transplant for the control group. The control group also experienced mean resorption activity above, and mean formation activity below pre-treatment levels. Therefore, results indicate that participation in an aerobic and resistance training program stimulated bone metabolism, through the uncoupling of bone turnover, favouring bone formation.

# CHAPTER EIGHT

## STUDY FIVE

### **Changes in QoL following a PBST and participation in an exercise program**

.....[Among the Greeks] eminent physicians say to a patient who come to them with bad eyes, that they cannot cure his eyes by themselves, but that if his eyes are to be cured, his head must be treated; and then again they say that to think of curing his head alone, and not the rest of the body also, is the height of folly. And arguing in this way they apply these methods to the whole body, and try to treat and heal the whole and the part together....

[The physicians for Thrace, however, criticize this and say that they are right as far as they go, but] that as you ought not to attempt to cure the eyes without the head, or the head without the eyes, neither ought to attempt to cure the body without the soul; and this...is the reason why the cure of so many diseases is unknown to the physicians of Hellas because they are ignorant of the whole, which ought to be studied also; for the part can never be well unless the whole is well.

PLATO, Charmides (Jowett translation)

**List of abbreviations specific to Chapter eight**

ADL	Activities of daily living
AS	Average severity
BMT	Bone marrow transplant
CARES	Cancer rehabilitation evaluation system
CG	Control group
EG	Exercise group
EP	Endorsed problems
FLIC	Functional living index-cancer
HRQoL	Health-related QoL
HOF	Higher order factors
KPS	Karnofsky performance scale
MQoL	Marital QoL
MIQoL	Medical interaction QoL
ND	Normative data derived from a cancer population
PBST	Peripheral blood stem cell transplant
PQoL	Physical QoL
PSQoL	Psychosocial QoL
QLI	Quality of life index
QoL	Quality of life
Rec Act	Recreational Activities
SG	Study group
SQoL	Sexual QoL
SS	Subscales under the physical domain
TQoL	Total QoL – which has been derived from the 5 QoL domains

## 8. Changes in QoL following a PBST and participation in an exercise program

---

### 8.0 Introduction

As a consequence of continuous progress in medical science, numerous previously fatal diseases are now curable and the severity of others has been effectively reduced<sup>172</sup>. With respect to cancer, the most recent estimate of the 5-year relative survival rate is now recognised to be 59%<sup>148</sup>. Unfortunately, medicine and science have failed to prevent the prolonged or permanent disabilities, which may arise from these conditions and their associated treatments.

Mortality and survival rates have commonly reflected the impact of new therapies on the disease process. However, as treatment modalities improve and the emphasis on humanising health care increases, these blunt and inadequate indicators are being replaced with quality of life (QoL) measures<sup>21, 171, 406</sup>. The belief that QoL is just as important as quantity of life is now widely accepted<sup>65</sup>. “Quality of life always matters to the patient and therefore, health care providers must always be concerned with the impact of their ministrations on the QoL in addition to the effect of the disease”<sup>73</sup>.

Cancer diagnosis and its associated treatments are associated with numerous physical and psychological side effects. The increased risk of late physical effects, psychological sequelae and social consequences have been identified as significant issues adversely influencing QoL<sup>272</sup>. Therefore, a strong need exists, for intervention strategies to assist in mitigating the adverse effects of cancer and its treatment on QoL, and/or hasten recovery following treatment. Physical exercise has been associated with numerous physiological and psychological health benefits within the healthy population. Exercise has also been shown to provide physical and psychological benefits during the rehabilitation process of patients with chronic diseases including cardiovascular diseases, rheumatic disease, diabetes mellitus and renal diseases. It is therefore possible to suggest that participation in a physical exercise program throughout the cancer continuum could address a broad range of

physical and psychological issues associated with diagnosis and treatment. Research to date regarding the role of exercise in the rehabilitation of cancer patients has been regarded as “positive but preliminary”<sup>78</sup>. There exists a need to replicate and extend the current research within the domain of cancer, exercise and QoL.

### 8.0.1 Purpose

Objective 1: To investigate changes between pre- and post-PBST measures of QoL.

*Research hypothesis for objective 1:*

Adverse changes will occur in QoL following a PBST (as determined by pre- and post-transplant measures).

Objective 2: To investigate the role of a three-month duration, moderate intensity, mixed type exercise program on QoL, post-PBST.

*Research hypothesis for objective 2:*

Participation in the exercise program will be associated with positive changes in QoL. That is, exercising patients will experience a faster QoL recovery when compared with non-exercising patients (as determined by pre- and post-intervention measures).

“The main point of using global QoL measures is that the more narrowly-defined objective (e.g. cardiovascular endurance) or subjective changes (e.g. anxiety) in functioning that may result from exercise following cancer diagnosis need ultimately to be reflected in the broad dimensions of QoL, or they may not have the practical benefit that is assumed”<sup>77</sup>. This thesis provides an excellent framework whereby physiological changes can be compared with QoL changes.

Objective 3: To investigate the relationship between functional capacity and QoL.

*Research hypothesis for objective 3:*

Functional capacity will be highly related to QoL. That is, those who experience the highest functional capacity will also experience the highest QoL.

## 8.1 Literature Review

The voluminous and growing body of scientific literature on QoL reflects the recent focus of interest on the integration of QoL end points in clinical trials of cancer therapies<sup>145</sup>. A consensus exists that QoL is a multidimensional construct, including a minimum of physical, social, and psychological domains in addition to disease- and treatment-related symptoms such as pain, shortness of breath, nausea, alopecia, anxiety or depression<sup>130, 131, 325</sup>. Existential concerns, sexual functioning, body image, and health care satisfaction are other important considerations when assessing QoL in cancer patients<sup>130</sup>. However, universal acceptance of one definition for QoL is lacking.

Quality of life has been defined as “subjective well-being”<sup>73</sup>, as “the subjective evaluation of life as a whole”, and “refers to patients’ appraisal of, and satisfaction with, their current level of functioning compared to what they perceive to be possible or ideal”<sup>130</sup>. “Conceptually, QoL has to do with the sense of satisfaction and well-being that an individual feels about his or her life, and qualities such as the degree to which an individual succeeds in accomplishing his desires and the extent to which a person’s hopes and ambitions are matched and fulfilled by experience”<sup>278</sup>. Recently, a World Health Organisation group proposed that “QoL can be defined as the individual’s perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns” - highlighting the emphasis on an individual’s judgement<sup>373</sup>.

Health related quality of life (HRQoL) is commonly defined as the “subjective experience of the impact of the disease on the quality of one’s life”<sup>400</sup>. This definition aims to provide a description of how the patient experiences their disease. Health-related QoL “describes the beliefs and behaviours of daily life which are governed by the degree of good or ill health that an individual, group or population experiences”, with the typical domains of HRQoL assessment including well-being, pain and discomfort, body image, sexuality, mobility and the ability to perform daily activities<sup>172</sup>. However, Avis and colleagues (1996)<sup>21</sup> noted that HRQoL generally denotes the aspects of life most likely to be influenced by health, including physical

and mental health; physical, social and cognitive functioning; intimacy or sexual functioning; and productivity.

During use in cancer clinical trials, QoL has been defined as “the ability to perform everyday activities which reflect physical, psychological and social well-being; and patient satisfaction with levels of functioning and control of disease and/or treatment-related symptoms”<sup>145</sup>. Similarly, it was stated that “QoL is a state of well-being which is a composite of two components including the ability to perform everyday activities which reflect physical, psychological and social well-being; and patient satisfaction with levels of functioning and control of disease and treatment-related symptoms”<sup>118</sup>.

Assessment of QoL provides valuable and relevant data that are useful for patients, clinicians, researchers and health policy makers<sup>25</sup>. These tools can prove useful in determining needs, developing intervention strategies and evaluating intervention outcomes<sup>213</sup>. Quality of life assessment can also identify patients’ needs, monitor the impact of treatment and assist in determining the need for specific services. The use of QoL tools as an outcome measure is a relatively new concept. However, it is commonly used in describing the nature and degree of the patient’s functional and psychosocial problems, in establishing norms of psychosocial morbidity, in monitoring the delivered quality of care, in evaluating intervention strategies, and in screening patients for the need for intervention strategies<sup>59</sup>.

Numerous HRQoL assessment tools exist and include global assessment, multi-attribute utility scales and multidimensional scales, which may be generic or disease-specific instruments<sup>169, 172, 213</sup>. The QoL tools that are disease-specific have the capacity to capture the unique problems and concerns in a particular population, and are extremely sensitive to small changes in QoL<sup>56, 132</sup>. A list of questionnaires specifically designed for use with cancer patients has been provided in Table 8.1. Although these questionnaires have been designated as cancer-specific, some of the measures could be, and at times have been, applied in other diseased populations<sup>65</sup>. Examination of the item content in some of these tools revealed that several of the concepts measured are generic rather than cancer-specific. A detailed review of each questionnaire has been provided elsewhere<sup>65</sup>.

**Table 8.1** Cancer-related QoL questionnaires

<p>Psychometric measures include:-</p> <ul style="list-style-type: none"> <li>➤ Functional Living Index-Cancer (FLIC)</li> <li>➤ Cancer Rehabilitation Evaluation System (CARES)</li> <li>➤ McGill questionnaire</li> <li>➤ Spitzer Quality of Life Index</li> <li>➤ Ferrans and Powers Quality-of-Life Index</li> <li>➤ Karnofsky Performance Scale (KPS)</li> <li>➤ European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core</li> <li>➤ Functional Assessment of Cancer Therapy</li> <li>➤ Linear-Analogue Self-Assessment scale</li> <li>➤ Rand 36-item survey 1.0</li> </ul>
<p>Utility Measures include:-</p> <ul style="list-style-type: none"> <li>➤ Quality-of-Well-Being Scale</li> <li>➤ Quality-adjusted Time Without Symptoms and Toxicity</li> </ul>

When deciding upon the most appropriate QoL questionnaire to use, factors relating to the patient population should be taken into consideration. As described in detail in Chapter 3, the subject group for this investigation included patients with a range of cancer diagnoses, who had been administered and/or were about to undergo a vast range of treatment options including surgery, chemotherapy and radiotherapy. As a consequence of the cancer and treatment undertaken, the patient group was at risk of numerous short- and longer-term side effects. It has also been recommended in the literature that the QoL measure should include questions that are relevant and simple to comprehend, while being sufficiently sensitive to changes in symptomatology or QoL<sup>65</sup>. Following careful consideration of these factors, the CARES questionnaire was deemed to be an effective and useful tool for use in this investigation.

The CARES is a standardised, comprehensive rehabilitation and QoL questionnaire designed specifically for use with cancer patients<sup>131</sup>. It has been administered to greater than 1100 cancer patients who have been diagnosed with various forms of cancer and who have undergone a diverse range of treatment regimens<sup>334</sup>. The theoretical background, item and scale development of the instrument have been

previously described in the literature<sup>334</sup>. The tool provides a global QoL score and global scores for 5 QoL domains, which are referred to as higher order factors (HOF). The 5 HOF are physical, psychosocial, medical interaction, marital and sexual. For each of these categories, further information is provided regarding the number of identified problems (which are referred to as endorsed problems) and the average severity rating of these identified problems.

Reliability studies<sup>335, 336</sup> performed on the CARES have demonstrated that the tool has excellent test-retest reliability. The initial reliability investigation calculated the Pearson product-moment correlation on three of the CARES summary scores and reported the *r* value to be greater than 0.84. Subsequent testing of the tool supported previous results, with all correlations being above 0.82. Between 84-88% of the time, the patients' second ratings agreed with their first ratings in determining whether a problem existed. Research on the content validity of the instrument has suggested that it is comprehensive and represents problems experienced by cancer patients<sup>336</sup>. Concurrent validity has also been assessed, and it was found that the CARES is measuring what it purports to measure<sup>336</sup>. Moreover, the CARES has been compared with the Dyadic Adjustment Scale, the KPS, a global measure of QoL using a 10-centimetre visual analogue scale and the FLIC. These investigations have demonstrated expected correlations and provide evidence of the concurrent and construct validity of the CARES<sup>334</sup>.

The CARES presents a detailed assessment of rehabilitation concerns, which makes it an ideal tool in research and clinical settings<sup>132</sup>. It is also capable of discriminating between different surgery techniques, as is evidenced by the segmental mastectomy breast cancer group scoring fewer problems than the modified radical mastectomy group<sup>132</sup>. Finally and importantly, the questionnaire is readily accepted by patients. This was determined through patient interviews, whereby the patients reported that the instrument was reflective of the cancer experience, was not offensive, was simple to comprehend and complete<sup>334</sup>.

In summary, the CARES meets a number of criteria for being a generic measure of QoL in cancer patients<sup>132</sup>. The global CARES score is sensitive enough to identify stage-related differences in cancer sites and cancer site differences for patients who

are at the same phase of disease. Furthermore, the summary scales of the CARES provide additional insight into the specific dimensions of QoL that reflect variations in known disease-specific problems<sup>132</sup>.

### **8.1.1 Quality of life of patients with cancer**

The majority of the population tends to equate cancer with death, and thus cancer is perceived as the worst illness of all medical conditions<sup>322</sup>. However, previous investigations reviewed by Ringdal et al (1994)<sup>322</sup> have compared the QoL of cancer populations to other diseased populations and to healthy subjects, and found contrasting results. Few studies were identified that were able to demonstrate that one or more QoL dimensions were substantially lower in the cancer population when compared with other clinical patient groups and healthy subjects. Some investigations reported that cancer patients were more satisfied with the care they received from their partner and 'significant others', and reported more positive and fewer negative social experiences, when compared with healthy persons. This was explained by changes in the way cancer patients value life and experiences. Although, it was also cautioned that patients may lower their aspirations and be satisfied despite their life being impaired.

There have also been differing results reported<sup>36, 383</sup>. Responses to 2 validated questionnaires assessing self-reported satisfaction with life and physical health, conducted among 204 long-term survivors of head and neck cancer, were compared with those responses from 766 matched controls<sup>36</sup>. It was found that, compared with the controls, cancer patients rated significantly lower satisfaction with life and physical health. Additionally, a QoL evaluation based on a number of questions covering general body symptoms, mood level and functional limitations, demonstrated that patients with gastric cancer reported more neurasthenic complaints such as reduced sexual interest, insomnia and poor appetite, in conjunction with a lower mood when compared with the general population<sup>383</sup>.

Comparisons between different cancer patient groups have also been made. The CARES QoL tool was utilised to investigate the QoL of patients with colorectal, breast, lung and prostate cancer<sup>132</sup>. A relationship between the global CARES score

and the extent of disease was found for the colorectal and lung cancer patients, whereby those patients experiencing the most extensive disease, maintained the least favourable global score. In this same patient group, the relationship described above was also found for the five HOF and extent of disease. The only exception was for the marital interaction summary scale in the lung cancer patient group. Similar results were reported in an investigation that compared the QoL of patients considered to have a good prognosis, with that of patients considered to have a medium or poor prognosis<sup>322</sup>. Patients with a good prognosis scored significantly higher on the general QoL-scale and on physical aspects of the QoL. Interestingly though, only marginal differences existed among the prognosis groups for the social and psychological aspects of QoL, such as emotional functioning (anxiety and depression).

A cross-sectional designed study was employed to assess the QoL in patients with lung, colon and prostate cancer, and who represented short-, intermediate- and long-term survivors<sup>333</sup>. While length of survival was not a critical factor in QoL ratings for the lung cancer patients, a clear positive association for length of survival and QoL was observed for colon cancer patients. Quality of life failed to improve with longer survival times in the prostate cancer group, with the survivors reporting poorer QoL globally. Additionally, functional status was a significant factor in QoL ratings for each of the cancers.

Differences between patients at the same phase of disease with colorectal, lung and prostate cancer have also been assessed<sup>132</sup>. For the patients with no evidence of disease, no significant difference was found between each of the different types of cancer groups. However, for the localised disease patients, patients with prostate cancer rated a higher QoL when compared with lung cancer patients. In the extensive disease patients, patients with prostate cancer scored a higher QoL than lung and colorectal cancer patients. In support of these findings, patients with advanced-stage lung cancer documented more physical functioning, psychosocial functioning and marital interaction problems and a lower global QoL when compared to patients with advanced-stage prostate cancer<sup>248</sup>.

Common factors listed by patients which influence QoL include diminished cardiovascular function, reduced strength and deterioration of lean body tissue, body composition changes, fatigue, pain, weakness, insomnia, gastrointestinal problems, shortness of breath, sweating and anorexia<sup>72, 77</sup>. Some of the more common psychological emotional sequelae of the cancer experience known to influence QoL include depression, anxiety, stress, reduced self-esteem, loss of sense of control and diminished psychological and emotional well-being<sup>77</sup>.

Anxiety and depression have been detected in many patients with a variety of malignancies who are receiving radiotherapy, both prior to treatment and 3–4 months post treatment<sup>69</sup>. With specific reference to breast cancer patients, evidence demonstrates that multiple factors including disturbances in body image and self-concept; social, sexual and family relationship disruptions; emotional distress; and the inability to maintain or resume normal daily activities - adversely influence QoL<sup>246</sup>. Psychosocial difficulties such as peer relationship problems, depression and altered self-concept and body image perceptions, are known factors influencing the QoL of adolescents following cancer diagnosis and treatment<sup>192</sup>. Exacerbating these issues are the presence of physical and functional problems such as reduced cardiovascular and pulmonary function, reduced exercise tolerance and changes in body composition. A number of specific factors likely to compromise post-BMT QoL include fatigue, weakness, occupational disability, sleep difficulties and sexual relationships and functioning<sup>13</sup>.

Impaired social functioning, physical functioning and work-related problems were reported in 20%, 33% and 20% of BMT patients, respectively<sup>424</sup>. Additionally, problems relating to physical, emotional, occupational and cognitive functioning have been associated specifically with allogenic transplant patients<sup>11</sup>. BMT patients reported more negative changes regarding physical health, when compared with changes to relationship and psychological status<sup>85</sup>. Allogenic transplant patients report poorer QoL when compared with autologous transplant patients, and greater age at BMT, lower education level and more advanced disease are also known risk factors for poorer QoL<sup>13</sup>. Finally, while some BMT recipients rated 'normal' QoL, the majority indicated a compromised QoL when compared to their premorbid status<sup>13</sup>.

More recent work has assessed the QoL in women with breast cancer undergoing autologous PBST<sup>206</sup>. Nine women, aged between 23–58 years completed two questionnaires - the Sickness Impact Profile and the Swedish HRQoL questionnaire - pre- and immediately post-transplant, and 7–15 weeks following the transplant. The results demonstrated that the women were adversely affected by the treatment in various dimensions of daily life. Undergoing the transplant particularly affected their self-rated health and function, and physical health status was perceived to be lowest at time of discharge, when compared with pre- and 7-15 weeks post-transplant. The emotional status for the breast cancer patients was also considered to be poor throughout the entire study period, when compared with matched controls.

Evidence clearly demonstrates that QoL is detrimentally affected as a consequence of cancer diagnosis and treatment. Cancer care should therefore include intervention strategies that have the potential to prevent, minimise and/or reverse these adverse effects.

### **8.1.2 Exercise and quality of life**

“Physical exercise is a fundamental aspect of quality of life”<sup>38</sup>. Impairment of physical fitness is a significant contributor to decrements in QoL in cancer patients<sup>105</sup> during and following conventional levels of cancer therapies<sup>77</sup>. It has been suggested that participation in a regular exercise intervention program may simultaneously influence many dimensions of QoL, or alternatively it may directly influence one dimension, which in turn has a ‘domino effect’ among other wellness domains<sup>445</sup>.

The physiological benefits of participation in regular exercise have been extensively reported in the previous chapters. Of specific importance to this investigation are the benefits derived through exercise participation, both physiological and psychological, that will lead to positive changes in QoL. Following a review of 24 empirical studies published between 1980 and 1997 regarding exercise, QoL and cancer, it was reported that studies have consistently demonstrated that physical exercise has a positive effect on QoL following cancer diagnosis<sup>77</sup>. Importantly, exercise was shown to induce a positive effect on physical, functional, psychological, emotional,

and social well-being. All these aspects lead to an overall improvement in global QoL.

A decrease in total mood disturbance<sup>226</sup>, sleep disturbance, depression, fatigue and nausea<sup>246</sup>, and an enhanced perceived internal locus of control<sup>124</sup>, self-esteem, self-confidence<sup>257</sup>, life satisfaction<sup>78</sup> and overall QoL<sup>445</sup>, have been reported among exercising cancer patients. Patients perceive exercise as a stress-controlling mechanism that assists them in coping with the disease<sup>426</sup>. It also allows patients to maintain a sense of control over their lives, including the maintenance or enhancement of fitness<sup>426</sup>.

The majority of work in the area of exercise, QoL and cancer has investigated patients with breast cancer. Following a 10-week cycle ergometry protocol of 3 sessions per week, breast cancer patients experienced reduced levels of nausea, anxiety and depression<sup>226</sup>. The exercising patients demonstrated a reduction in fatigue in conjunction with elevated feelings of vigour, while the control group showed a worsening of mood states<sup>226</sup>. Others have reported that exercise may induce positive mood changes, body image, self-esteem, confidence, personal worth, self-acceptance, and control, while reducing depression, tension, anxiety, anger, helplessness, hostility and pessimism<sup>246, 369</sup>. Women with breast cancer have demonstrated that those who exercise regularly experience a significantly higher QoL when compared with matched controls<sup>445</sup> and that the improvement in quality of life is proportional to the amount of exercise undertaken<sup>291</sup>.

Others have investigated the role of exercise (a self-paced, progressive walking program) during radiation treatment and have also found positive results<sup>247</sup>. Outcome measures evaluated included physical functioning (as assessed by the 12-minute walk test) and fatigue, anxiety, depression and difficulty sleeping. Eighty-six per cent of the experimental group maintained the active exercise program throughout the entire duration of treatment. While anxiety, depression and difficulty sleeping were common symptoms for both groups, the control group experienced greater symptom intensity. Additionally, while both groups reported high levels of dissatisfaction with their body, the symptom was correlated with fatigue, anxiety, depression and difficulty sleeping.

The potential for physical activity to address QoL issues in adolescents with cancer has only recently been investigated<sup>192</sup>. Those adolescents who maintained their organised sport participation throughout the entire cancer experience (diagnosis, treatment and post-treatment) reported physical benefits and also noted better general self-concept, physical abilities, as well as parental, same-sex and opposite-sex relationships<sup>192</sup>. Importantly, these are some of the primary psychosocial outcomes compromised in adolescents following cancer diagnosis. It was further suggested that participation in organised sport may provide adolescents with invaluable opportunities for normalising physical, functional, social and psychological well-being.

There have been only a few recent studies regarding the role of exercise in patients undertaking a BMT. Participation in exercise by BMT patients during hospitalisation has been significantly correlated with all QoL indices, except emotional and social well-being<sup>80</sup>. The most consistent relationships were identified for physical well-being, depression, anxiety and psychological well-being. Significantly fewer medical complications, including duration of neutropenia and thrombocytopenia, and severity of diarrhoea and pain - all of which may relate to improved QoL - have also been found in exercising BMT patients<sup>102</sup>.

An aerobic exercise program implemented in patients receiving high-dose chemotherapy followed by autologous PBST, showed that there can be positive effects on the mental status of cancer patients and that the effects of physical activity are not limited to improved physical performance alone<sup>105</sup>. Patients in Dimeo et al's study (1995)<sup>105</sup> were divided into a control and training group, with the training program consisting of daily, discontinuous duration of exercise using a bed ergometer at an intensity of at least 50% cardiac reserve, for the duration of their hospital stay. Improvements in the training group were shown in several indicators of psychological distress including depression, fear, anger/hostility, interpersonal sensitivity and phobic anxiety in the training group<sup>105</sup>. While several psychological distress scores were reduced in a number of areas for the exercising patients, the control group showed no improvement in mood state. In addition, unlike the training

group, the control group demonstrated a significant rise in fatigue and somatisation scores by the time of hospital discharge.

The importance of the above findings are highlighted further when it is taken into account that depressed mood, functional QoL and mental adjustment have been previously linked to survival in BMT patients and other cancer patient groups<sup>12</sup>. An attitude toward cancer characterised by 'anxious preoccupation', in addition to poorer functional QoL, have each been associated with poorer post-BMT survival. Better functional QoL was related to longer survival.

### **8.1.3 Relationship between functional capacity and quality of life**

The effectiveness of common intervention strategies currently available for patients with cancer such as relaxation training, meditation, professional support/counselling, social support and alternative treatments such as music therapy, in improving QoL, was assessed via a meta-analysis<sup>77</sup>. While the treatment categories were considered to be equally effective, they illustrated the weakest effect for functional QoL. The results of this investigation are particularly significant when the results of other research are also taken into account. A negative change in physical health has the greatest impact on overall QoL, when compared with changes in the other QoL domains<sup>22, 78</sup>. This overlapping nature of health and functional status is commonly observed when individuals define their state of health by stating what they are capable and not capable of performing<sup>22</sup>. Importantly, while the functional and physical domain of QoL has been reported to be the most important QoL dimension underlying overall satisfaction with life, it is often the least possessed<sup>78</sup>.

The strong relationship between physical QoL and global QoL underscores the potential inadequacies of current QoL interventions that fail to practically address the physical concerns of the patient<sup>80</sup>.

## **8.2 Methodology**

Chapter 3 provides a detailed outline of the methodological procedures that relate to subject recruitment, the testing phases and the intervention program implemented. In summary, 12 patients, with 6 patients in each group were recruited. Of these, only 7 patients were recruited at PI, while the remaining subjects entered the investigation at PII. Outlined below are the methodological procedures, which relate specifically to the aims of this section of the investigation and involve the assessment of total QoL and 5 QoL domains.

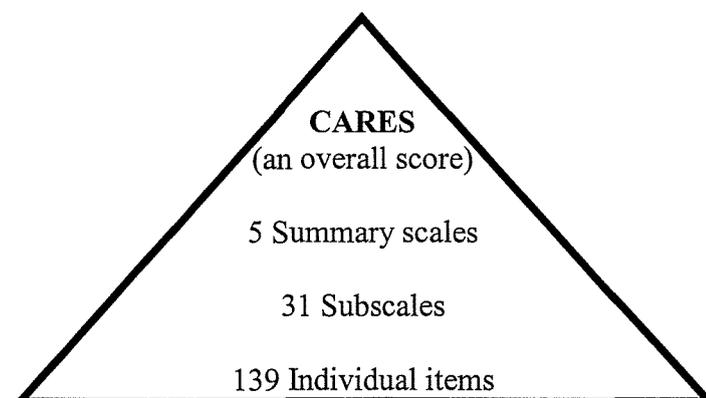
### **8.2.1 Quality of life assessment**

The Cancer rehabilitation evaluation system (CARES) (Appendix VIII) was used to assess QoL. The CARES consists of 139 'problem statements' (which are referred to as items), 88 of which are completed by all patients, while the remaining 51 items are only completed by patients when relevant. In total, a minimum of 93 items, and a maximum of 132 items may apply to any one patient. Patients completing the questionnaire are required to read each statement and provide a rating regarding how much the statement applies to them. The CARES utilises a 5-point rating scale, ranging from 0 (the statement does not apply at all) to 4 (the statement applies very much) during the past month. Due to the nature of the scoring system, a lower score corresponds with a higher QoL rating.

The CARES can be scored in several ways, with the most detailed level of scoring consisting of 31 subscales and 7 remaining miscellaneous items. A broader overview scoring consists of a global QoL rating and global ratings for the 5 higher order factors or summary scales, including physical, psychosocial, medical interaction, marital and sexual.

The level of scoring is represented in Figure 8.1, while a summary of the items which comprise the 5 summary scales (or QoL domains) has been presented in Appendix IX.

**Figure 8.1** Scoring the CARES



Five types of scores (presented below) can be calculated in the three top levels of the pyramid. Obviously, the more scores that are calculated, the greater the detail obtained.

- 1) ***The severity rating*** which represents a summation of all items within a scale rated between 1 and 4.
- 2) ***The number (#) of potential problems*** which represents the number of items that maintains the potential of applying to a particular patient for each scale.
- 3) ***The number (#) of endorsed problems (EP)*** which represents the number of items that have the potential of applying to a particular patient and has received a rating between 1 and 4.

These three scores were then used to generate the ***average severity rating (AS)*** and the ***global score (QoL score)***.

4) ***Average severity rating*** = 
$$\frac{\text{severity rating}}{\# \text{ of endorsed problems}}$$

5) ***Global score*** = 
$$\frac{\text{severity rating}}{\# \text{ of potential problems}}$$

The patients' responses between 1 and 4 in the CARES booklet were transferred to the CARES Score and Profile Sheet (appendix X). The three preliminary scores (Severity Rating, # of Endorsed Problems, and # of Potential Problems) were calculated for each summary scale and transferred to the bottom right corner on the score sheet, where the final calculations were made. The average severity rating and

the global score were then calculated. Following the computation of the raw scores, the data were then converted to T scores using the tables provided in the CARES manual<sup>76</sup>, and were then used in the statistical analysis. The T scores allowed for the comparison of data with 'normative' cancer population data, again provided in the CARES manual<sup>76</sup>. The normative data were derived from 1047 American outpatients and included patients of various ages, socioeconomic status, marital status, ethnicity, disease diagnosis, and treatment regimens undertaken.

In summary a global score, number of endorsed problem score and average severity score were calculated for total QoL, and physical, psychosocial, medical interaction, marital and sexual QoL. The number of endorsed problems and average severity rating were also calculated for the 7 subscales within the physical QoL domain.

### **8.2.2 Statistical analysis**

QoL data were collected at each of the three testing phases and were analysed according to the statistical procedures outlined in Chapter 3. Additionally, the relationship between functional capacity and QoL was assessed by correlating (Pearson correlation) aerobic capacity (measured in ml/FFM/min as outlined in Chapter 5) and QoL measures at PI, PII and PIII. The QoL measures included in the analysis were total and physical QoL, number of endorsed problems relating to total and physical QoL, and average severity of endorsed problems relating to total and physical QoL. Psychosocial, medical interaction, marital and sexual QoL were also included in the correlations.

### 8.3 Results

Significant adverse changes in total QoL ( $p < 0.05$ ) were associated with undergoing an autologous PBST (Table 8.2). Physical, psychosocial, medical interaction and sexual QoL domains were also affected, however the changes were not significant. With the exception of the sexual QoL domain, an elevation in the mean number of endorsed problems, as well as an increase in the mean average severity of the problem, contributed to these poorer global scores. Contributing to the mean change observed in the sexual global score was an increase in the number of endorsed problems, in addition to a significant reduction ( $p < 0.05$ ) in the average severity of the problems.

**Table 8.2** QoL measures at PI and PII for the study group (mean $\pm$ SE)

SG	PI n = 7		PII n = 12		p value
	Mean	SE	Mean	SE	
Total QoL (TQoL)	54.17	1.21	57.75	0.74	0.024*
EP	56.64	1.43	57.92	0.87	0.457
AS	51.31	3.03	54.92	1.86	0.326
<b>QoL Domains</b>					
Physical QoL (PQoL)	56.42	2.09	61.17	1.28	0.071
Physical EP	58.25	2.16	61.58	1.33	0.209
Physical AS	54.14	1.88	58.50	1.15	0.066
Psychosocial QoL (PSQoL)	51.50	1.41	54.50	0.87	0.090
Psychosocial EP	54.56	1.78	55.67	1.09	0.603
Psychosocial AS	48.25	1.73	51.58	1.06	0.121
Medical Interaction QoL (MIQoL)	51.63	1.40	53.83	0.86	0.202
Medical Interaction EP	52.33	1.21	55.00	0.74	0.080
Medical Interaction AS	53.42	1.31	54.83	0.80	0.372
Marital QoL (MQoL)	53.11	1.23	53.25	0.75	0.924
Marital EP	54.19	0.89	53.33	0.54	0.420
Marital AS	50.86	1.42	52.33	0.87	0.393
Sexual QoL (SQoL)	54.75	1.32	57.50	0.81	0.097
Sexual EP	53.17	1.87	57.00	1.14	0.100
Sexual AS	60.89	1.70	56.33	1.04	0.037*

\*  $p < 0.05$

Undergoing a PBST was also associated with adverse changes in the number of endorsed problems and average severity of the problems in the physical subscales (Table 8.3). With the exception of pain and difficulty working, the mean number of endorsed problems increased following the transplant, with significant changes observed in the subscale of weight loss ( $p < 0.05$ ). Unlike the other subscales, the number of endorsed problems regarding difficulty working was significantly lower at PII ( $p < 0.05$ ), when compared with PI. The average severity of the endorsed problems also increased following the transplant, with the exception of the pain subscale. The change was significant for the subscales of ambulation ( $p < 0.05$ ), weight loss ( $p < 0.05$ ) and difficulty working ( $p < 0.01$ ).

**Table 8.3** Physical subscale measures at PI and PII for the study group (mean±SE)

SG	PI Mean	n = 7 SE	PII Mean	n = 12 SE	p value
<b>Physical subscales:</b>					
Ambulation EP	3.31	0.27	3.42	0.17	0.731
Ambulation AS	2.09	0.23	2.74	0.14	0.030*
Activities of daily living EP	1.94	0.25	2.42	0.15	0.122
Activities of daily living AS	1.20	0.29	1.88	0.18	0.065
Weight loss EP	1.97	0.46	3.17	0.21	0.031*
Weight loss AS	0.88	0.38	1.93	0.17	0.024*
Recreational activities EP	2.94	0.42	3.00	0.25	0.911
Recreational activities AS	2.04	0.31	2.38	0.19	0.376
Pain EP	2.17	0.45	1.33	0.27	0.130
Pain AS	1.22	0.37	1.04	0.22	0.694
Difficulty working EP	3.17	0.46	1.67	0.28	0.013*
Difficulty working AS	1.89	0.35	3.25	0.22	0.005**
Clothing EP	1.11	0.27	1.33	0.16	0.485
Clothing AS	0.90	0.37	1.26	0.22	0.414

\*  $p < 0.05$ , \*\*  $p < 0.01$

As shown in Table 8.4, both the EG and CG demonstrated a similar mean change across the phases for total QoL. Undertaking a transplant was associated with a reduction in total QoL, and a 3-month recovery period was associated with significant improvements in QoL ( $p < 0.01$ ). As is evident in Figure 8.2, the changes in the group mean are representative of individual changes. That is, all patients in both the CG and EG demonstrated the same trend of change between PI and PII, and PII and PIII. Both groups recorded mean QoL scores at PIII that were lower than PI, however, the difference was only significant for the EG ( $p < 0.01$ ). Although little change existed between the mean number of endorsed problems and average severity of the problems across the phases for the CG, the exercising patients demonstrated significant improvements ( $p < 0.01$ ) by 3-months post-transplant. Following the intervention period, significantly fewer endorsed problems ( $p < 0.01$ ) and less severe endorsed problems ( $p < 0.01$ ) were reported by the EG when compared with pre- and immediately post-transplant.

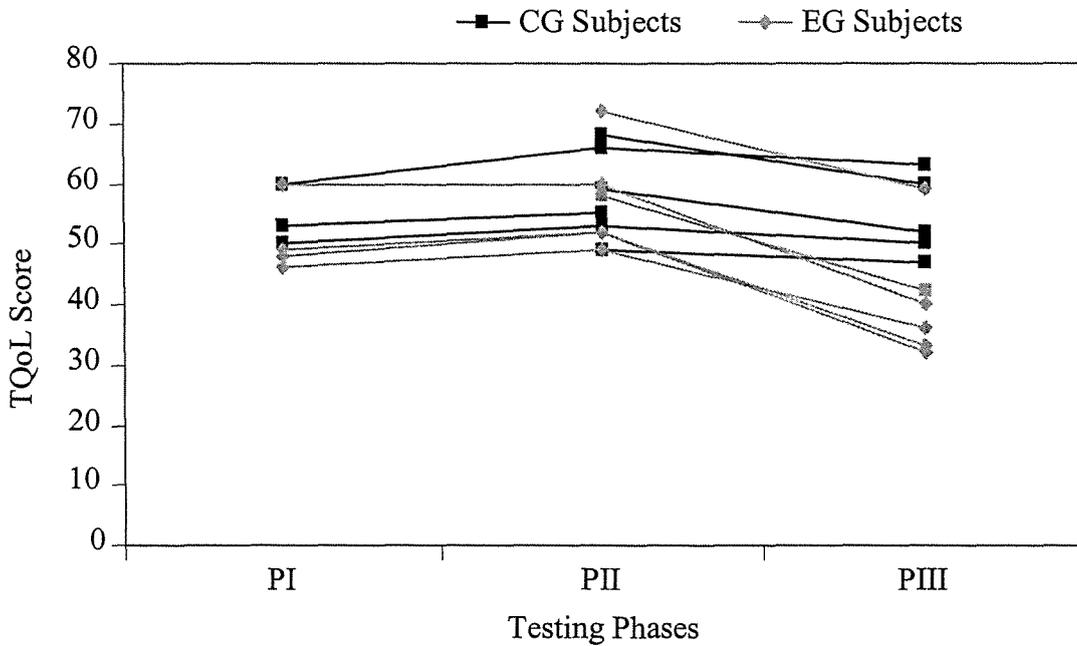
**Table 8.4** Total QoL measures across the testing phases for the control and exercise group (mean $\pm$ SE)

Total QoL	Phase	Mean	SE	Comparison	p value
<b>CG</b>					
TQoL	I	55.33	2.19	PI – PII	0.131
	II	58.33	1.05	PI – PIII	0.445
	III	53.83	1.21	PIII – PII	0.009**
TQoL EP	I	60.28	2.53	PI – PII	0.571
	II	59.67	1.24	PI – PIII	0.133
	III	58.31	1.43	PIII – PII	0.097
TQoL AS	I	50.44	5.46	PI – PII	0.328
	II	54.33	2.62	PI – PIII	0.678
	III	48.72	3.03	PIII – PII	0.065
<b>EG</b>					
TQoL	I	53.00	1.05	PI - PII	0.032*
	II	57.17	1.05	PI - PIII	0.000**
	III	40.33	1.05	PIII - PII	0.000**
TQoL EP	I	53.00	1.24	PI - PII	0.162
	II	56.17	1.24	PI - PIII	0.000**
	III	42.00	1.24	PIII - PII	0.000**
TQoL AS	I	52.17	2.62	PI - PII	0.453
	II	55.50	2.62	PI - PIII	0.007**
	III	37.67	2.62	PIII - PII	0.002**

n = CG: PI-3, PII-6, PIII-5; EG: PI-4, PII-6, PIII-6

\*  $p < 0.05$ , \*\*  $p < 0.01$

**Figure 8.2** Individual changes in total QoL across the testing phases for the subjects in the control and exercise groups



Although the CG and EG demonstrated similar changes across the testing phases for physical QoL, the changes were only significant for the exercising patients (Table 8.5). The 3-month exercise intervention period was associated with significant improvements in physical QoL ( $p < 0.01$ ), endorsed problems ( $p < 0.01$ ) and average severity of the problems ( $p < 0.01$ ). Further, scores for all 3 variables were significantly lower ( $p < 0.01$ ) at PIII, when compared with PI, for the exercising patients.

The changes observed in physical QoL can be attributed to changes in the physical subscales. Across the phases, little change was observed in the number of endorsed problems and average severity of the problems for the CG (Figures 8.3a, 8.4a), with the exception of difficulty working. At PIII, the CG scored a significantly lower average severity of problems in the difficulty working subscale ( $p < 0.05$ ). In comparison, significant improvements in the number of endorsed problems and average severity of the problems in the physical subscales were observed for the exercising patients (Figure 8.3b, 8.4b). Following the exercise program, patients rated significantly fewer problems for ambulation ( $p < 0.05$ ), activities of daily living (ADL) ( $p < 0.05$ ), weight loss ( $p < 0.01$ ), recreational activities (Rec Act) ( $p < 0.01$ ),

difficulty working ( $p < 0.05$ ) and clothing ( $p < 0.05$ ). By PIII scores were significantly lower when compared with PI, for the ambulation ( $p < 0.05$ ), weight loss ( $p < 0.01$ ), recreational activities ( $p < 0.05$ ), and difficulty working ( $p < 0.01$ ) subscales. The average severity of the problems in the subscales of ambulation, weight loss, recreational activities, difficulty working and clothing was also significantly lower by PIII ( $p < 0.05$ , except for the clothing subscale where  $p < 0.01$ ). Finally, exercising patients perceived the average severity of their endorsed problems to be significantly less than PI for the subscales of ambulation ( $p < 0.01$ ), recreational activities ( $p < 0.05$ ) and difficulty working ( $p < 0.01$ ).

**Table 8.5** Physical QoL measures across the testing phases for the control and exercise group (mean±SE)

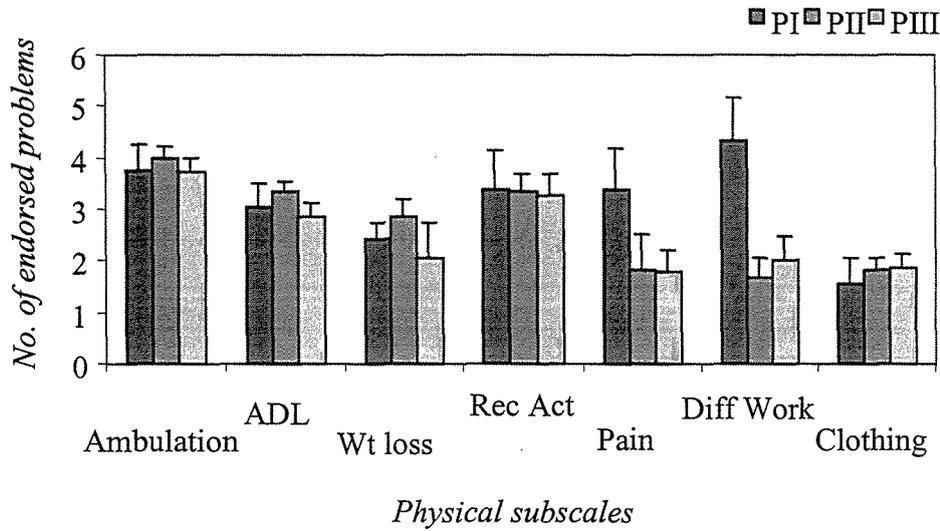
Physical QoL domain	Phase	Mean	SE	Comparison	p value
<b>CG</b>					
PQoL	I	59.83	3.76	PI - PII	0.401
	II	64.50	1.81	PI - PIII	0.842
	III	58.67	2.09	PIII - PII	0.143
PQoL EP	I	63.00	3.90	PI - PII	0.507
	II	66.17	1.87	PI - PIII	0.857
	III	62.08	2.16	PIII - PII	0.223
PQoL AS	I	56.28	3.39	PI - PII	0.390
	II	60.33	1.63	PI - PIII	0.668
	III	54.14	1.88	PIII - PII	0.082
<b>EG</b>					
PQoL	I	53.00	1.81	PI - PII	0.055
	II	57.83	1.81	PI - PIII	0.001**
	III	42.83	1.81	PIII - PII	0.000**
PQoL EP	I	53.50	1.87	PI - PII	0.210
	II	57.00	1.87	PI - PIII	0.004**
	III	43.67	1.87	PIII - PII	0.000**
PQoL AS	I	52.00	1.63	PI - PII	0.051
	II	56.67	1.63	PI - PIII	0.003**
	III	43.83	1.63	PIII - PII	0.000**

n = CG: PI-3, PII-6, PIII-5; EG: PI-4, PII-6, PIII-6

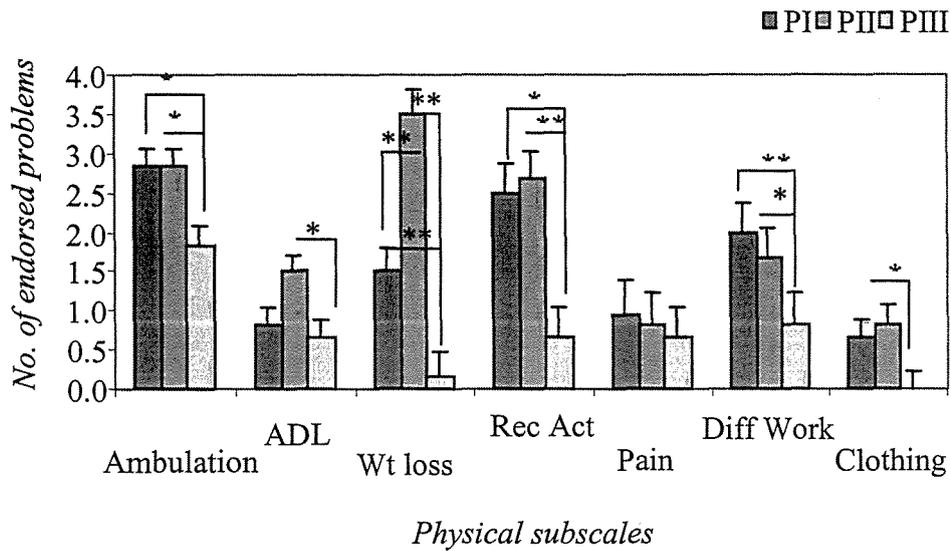
\*\*  $p < 0.01$

**Figure 8.3** Number of endorsed problems in the physical subscales, across the testing phases (mean±SE)

(a) Control group data (n = PI-3, PII-6, PIII-5)



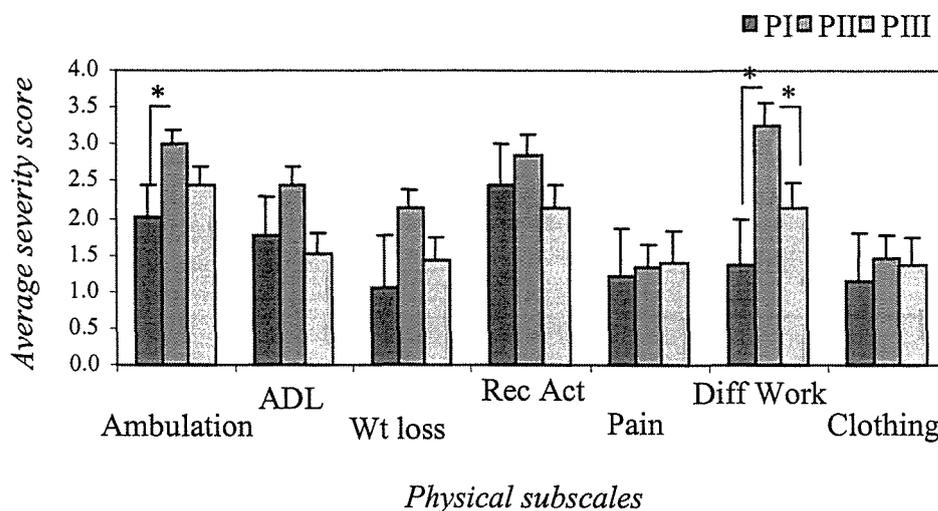
(b) Exercise group data (n = PI-4, PII-6, PIII-6)



\* p<0.05, \*\* p<0.01

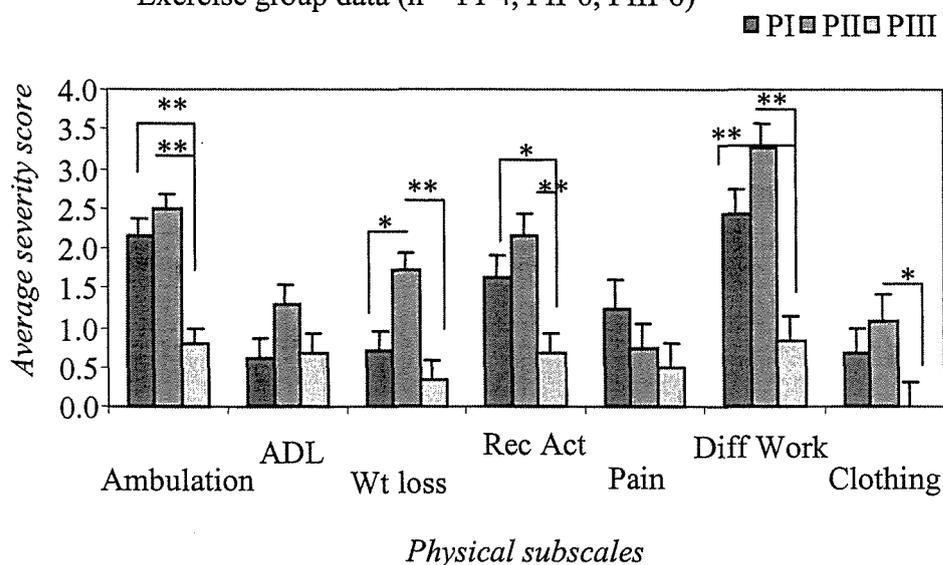
**Figure 8.4** Average severity of the endorsed problems in the physical subscales, across the testing phases (mean±SE)

(a) Control group data (n = PI-3, PII-6, PIII-5)



\* p<0.05

(b) Exercise group data (n = PI-4, PII-6, PIII-6)



\* p<0.05, \*\* p<0.01

As shown in Table 8.6, undertaking a PBST was associated with adverse changes in the global, EP and AS scores for the psychosocial domain, while a 3-month recovery period was associated with improvements in these scores. However, following the transplant, changes were only significant for the exercising patients (p<0.01). Further, following the 3-month intervention program, the exercising patients rated a significantly improved global (p<0.01), EP (p<0.01) and AS score (p<0.01), when compared with pre-transplant scores.

**Table 8.6** Psychosocial QoL measures across the testing phases for the control and exercise group (mean±SE)

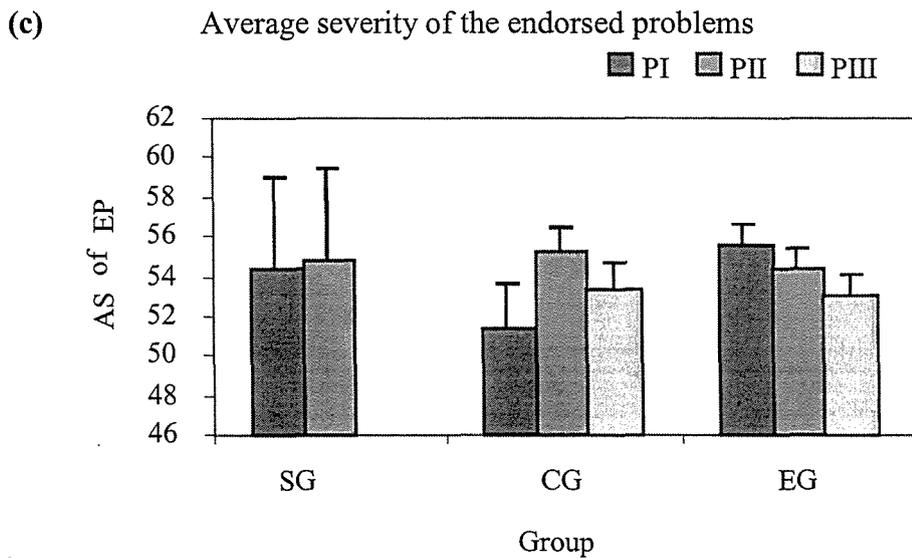
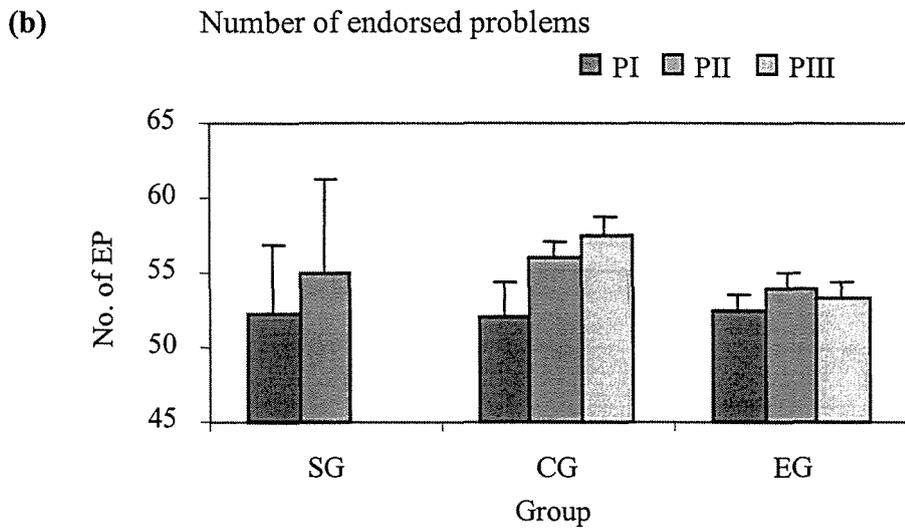
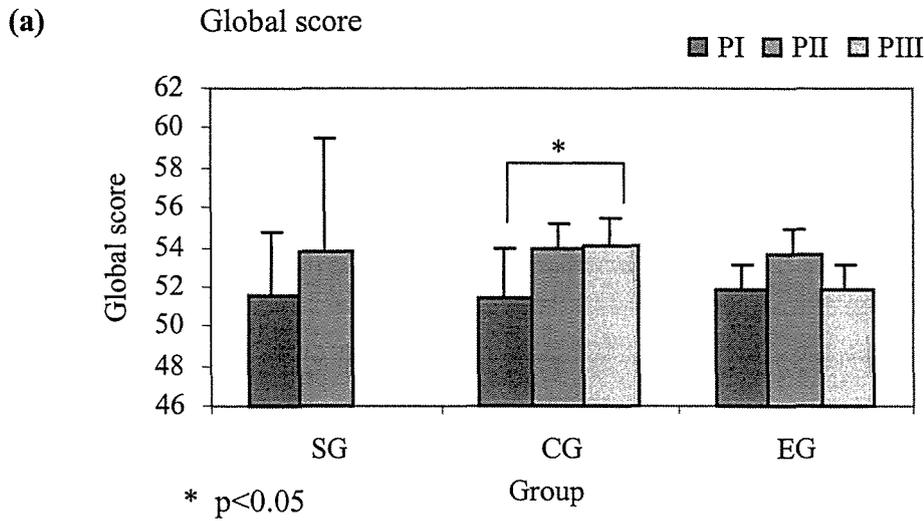
Psychosocial QoL domain	Phase	Mean	SE	Comparison	p value
<b>CG</b>					
PSQoL	I	49.33	2.55	PI - PII	0.036*
	II	54.00	1.22	PI - PIII	0.120
	III	52.67	1.41	PIII - PII	0.272
PSQoL EP	I	56.61	3.22	PI - PII	0.796
	II	57.17	1.55	PI - PIII	0.558
	III	55.22	1.78	PIII - PII	0.208
PSQoL AS	I	42.83	3.12	PI - PII	0.364
	II	49.67	1.50	PI - PIII	0.105
	III	48.25	1.73	PIII - PII	0.434
<b>EG</b>					
PSQoL	I	53.67	1.22	PI - PII	0.519
	II	55.00	1.22	PI - PIII	0.000**
	III	42.00	1.22	PIII - PII	0.000**
PSQoL EP	I	52.50	1.55	PI - PII	0.524
	II	54.17	1.55	PI - PIII	0.005**
	III	43.50	1.55	PIII - PII	0.002**
PSQoL AS	I	53.67	1.50	PI - PII	0.945
	II	53.50	1.50	PI - PIII	0.005**
	III	45.17	1.50	PIII - PII	0.005**

n = CG: PI-3, PII-6, PIII-5; EG: PI-4, PII-6, PIII-6

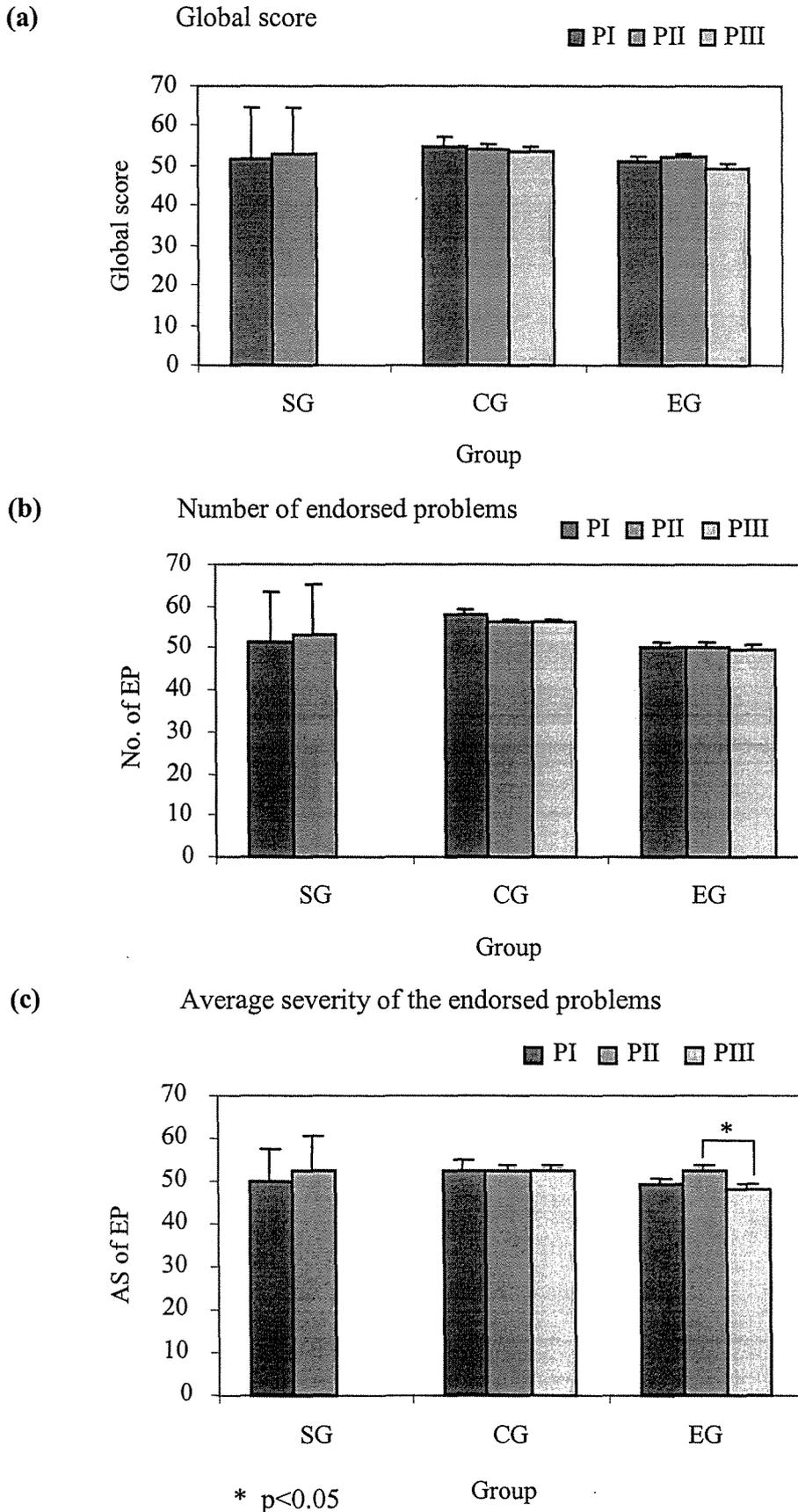
\* p<0.05, \*\* p<0.01

Medical interaction QoL (Figure 8.5a, b and c) and marital QoL (Figure 8.6a, b and c) showed few changes for both groups across the testing phases. Significant differences were only observed between the number of endorsed problems for medical interaction QoL at PI and PIII for the CG (p<0.05), and between the average severity of marital problems for the exercising patients at PII and PIII (p<0.05). Mean changes in sexual QoL were similar across the phases for both the exercising and non-exercising subjects (Figure 8.7a, b & c). The global sexual QoL score significantly improved following 3-months post-transplant for the CG (p<0.01) and EG (p<0.01). Additionally, the exercising patients rated significantly fewer problems following the intervention period when compared with the ratings recorded at PII (p<0.05). Although the CG demonstrated an improved average severity of the problems by PIII when compared with PI (p<0.05), the exercising patients rated a significantly lower average score at PIII when compared with both pre- (p<0.05) and immediately post- transplant scores (p<0.05).

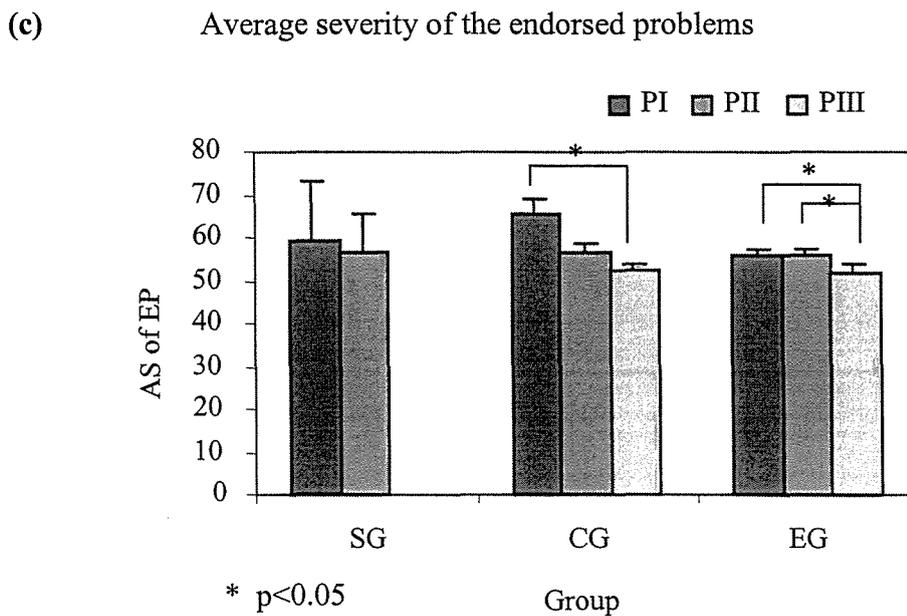
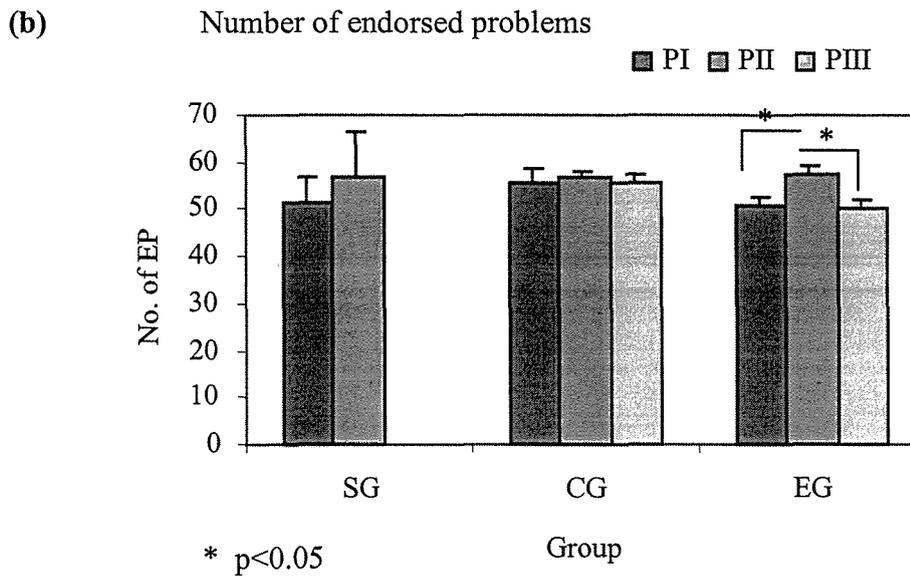
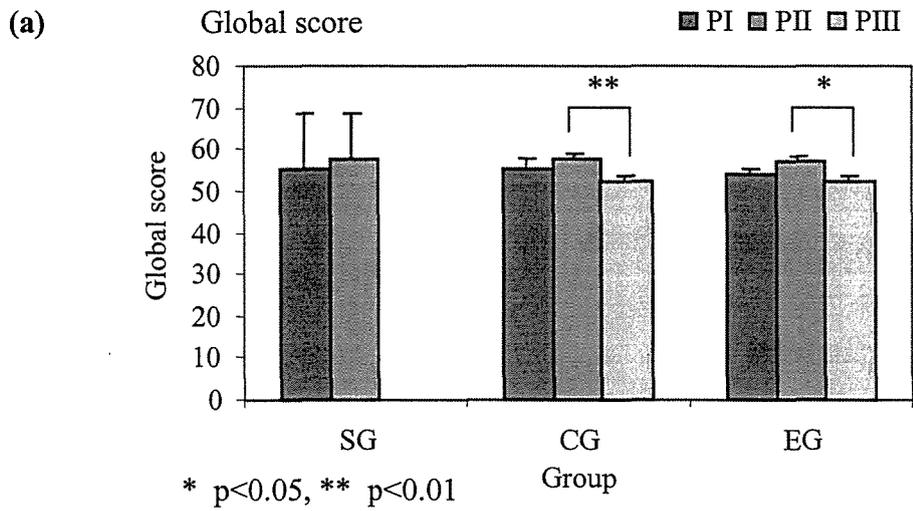
**Figure 8.5** Medical interaction QoL measures for the study group (PI & PII) and the control and exercise group (PI, PII & PIII) (mean±SE)



**Figure 8.6** Marital QoL measures for the study group (PI & PII) and the control and exercise group (PI, PII & PIII) (mean±SE)



**Figure 8.7** Sexual QoL measures for the study group (PI & PII) and the control and exercise group (PI, PII & PIII) (mean±SE)



Following the 3-month intervention program, those patients who participated in the exercise program reported a higher total QoL ( $p<0.05$ ) and fewer endorsed problems ( $p<0.05$ ) when compared with non-exercising participants (Table 8.7). Additionally, participation in the exercise intervention was also associated with higher physical QoL ( $p<0.01$ ) and psychosocial QoL ( $p<0.05$ ). Significantly fewer physical problems were endorsed ( $p<0.01$ ) and the average severity of the endorsed problems was lower ( $p<0.05$ ) for those in the EG when compared with the CG, by PIII. More specifically, in the physical domain the exercising patients demonstrated on average, fewer endorsed problems and less severe problems for all of the physical subscales (Table 8.8). These differences were significant ( $p<0.05$ ), with the exception of ambulation EP, activities of daily living AS, weight loss AS, pain EP, and difficulty working EP.

**Table 8.7** Comparisons between the control and exercise group at PIII, for total QoL and QoL domain measures (mean $\pm$ SE)

Variable	CG		EG		p value
	Mean	SE	Mean	SE	
CARES Global	53.83	1.21	40.33	1.05	0.025*
CARES EP	58.31	1.43	42.00	1.24	0.036*
CARES AS	48.72	3.03	37.67	2.62	0.080
Physical Global	58.67	2.09	42.83	1.81	0.004**
Physical EP	62.08	2.16	43.67	1.87	0.001**
Physical AS	54.14	1.88	43.83	1.63	0.037*
Psychosocial Global	52.67	1.41	42.00	1.22	0.028*
Psychosocial EP	55.22	1.78	43.50	1.55	0.059
Psychosocial AS	48.25	1.73	45.17	1.50	0.309
Medical interaction Global	54.06	1.40	51.83	1.21	0.250
Medical interaction EP	57.58	1.21	53.33	1.05	0.232
Medical interaction AS	53.33	1.05	53.00	1.14	0.662
Marital Global	53.28	1.23	49.50	1.06	0.620
Marital EP	56.19	0.89	49.83	0.77	0.456
Marital AS	52.53	1.43	48.00	1.24	0.271
Sexual Global	52.25	1.32	52.17	1.15	0.735
Sexual EP	55.58	1.87	50.33	1.62	0.491
Sexual AS	52.14	1.70	52.00	1.47	0.816

\*  $p<0.05$

\*\*  $p<0.01$

**Table 8.8** Comparison between the control and exercise group at PIII for the physical subscale measures (mean±SE)

Variable	CG		EG		p value
	Mean	SE	Mean	SE	
Ambulation EP	3.72	0.27	1.83	0.23	0.066
Ambulation AS	2.46	0.23	0.79	0.20	0.016*
Activities of daily living EP	2.86	0.25	0.67	0.21	0.006**
Activities of daily living AS	1.51	0.29	0.67	0.25	0.111
Weight loss EP	2.03	0.35	0.17	0.30	0.005**
Weight loss AS	1.44	0.29	0.33	0.24	0.099
Recreational activities EP	3.53	0.42	0.67	0.36	0.000**
Recreational activities AS	2.13	0.31	0.67	0.27	0.011*
Pain EP	1.78	0.44	0.67	0.38	0.188
Pain AS	1.39	0.43	0.50	0.31	0.040*
Difficulty working EP	2.00	0.46	0.83	0.39	0.156
Difficulty working AS	2.14	0.35	0.83	0.31	0.042*
Clothing EP	1.86	0.27	0.00	0.23	0.000**
Clothing AS	1.38	0.37	0.00	0.32	0.000**

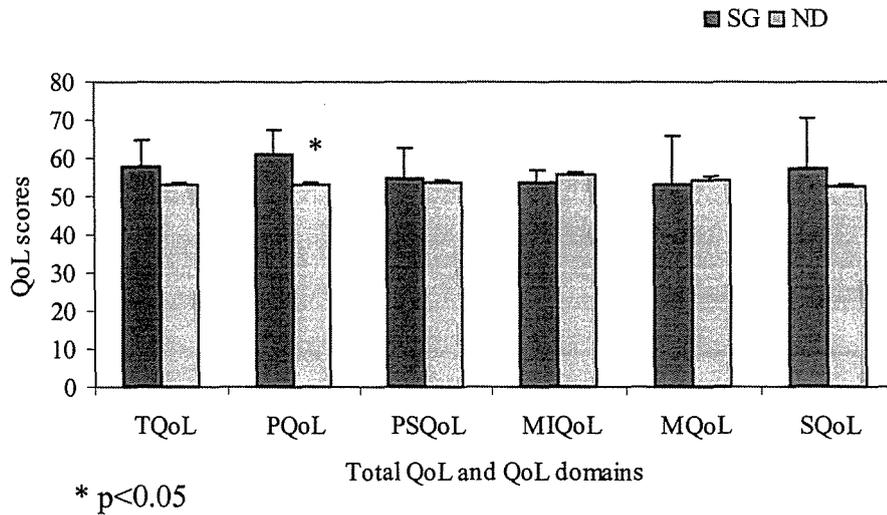
\* p&lt;0.05

\*\* p&lt;0.01

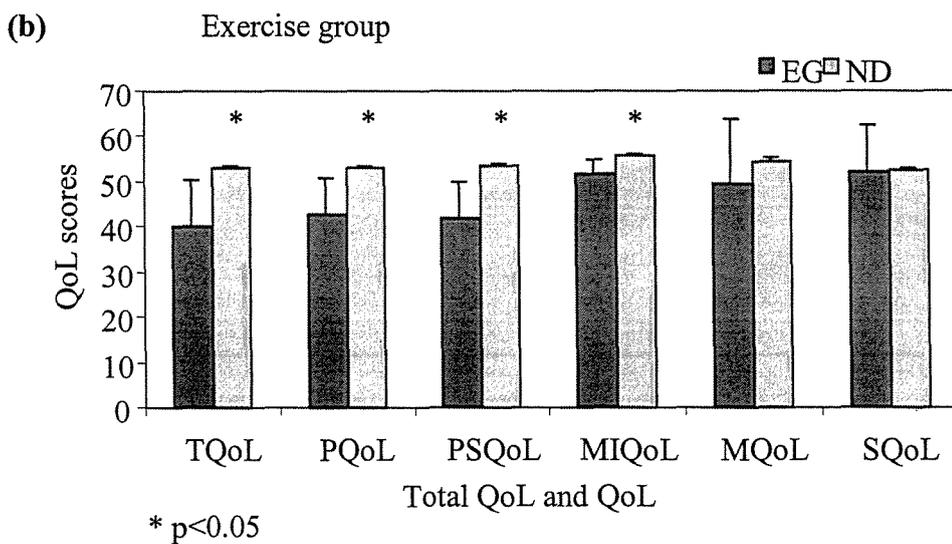
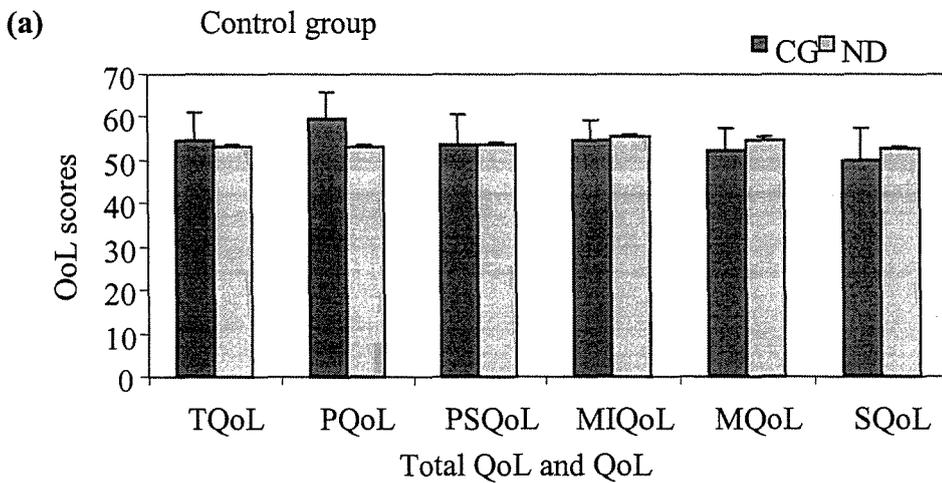
The PII and PIII QoL scores derived from the subject sample of this investigation were compared with normative data derived from a cancer patient population (Figure 8.8, 8.9a and b). At PII, PBST patients were, on average, experiencing a lower total QoL, and a significantly lower physical QoL, when compared with other cancer patients (Figure 8.8).

By 3-months post-transplant, the mean scores attained by the CG for total QoL, physical QoL, and psychosocial QoL remained higher than the normative cancer data, however the differences were not significant (Figure 8.9a). In comparison, the exercising transplant patients scored lower total QoL and QoL domain ratings than the normative cancer group, with significant differences being observed for total QoL and the QoL domains, physical, psychosocial and medical interaction (Figure 8.9b).

**Figure 8.8** Comparisons of total QoL and QoL domain measures at PII between the study group and normative cancer data (mean±SD)



**Figure 8.9** Comparisons of total QoL and QoL domain measures at PIII between the control and exercise group, and normative cancer data (mean±SD)



Finally, it was an objective of this investigation to determine the relationship between functional capacity (as measured by aerobic capacity) and QoL, and changes in functional capacity and QoL experienced between PI and PII. Aerobic capacity measurements and changes across phases have been described in detail in Chapter 5. The results presented in Table 8.9 demonstrate that those who were experiencing a higher level of fitness were more likely to experience a higher QoL, endorse fewer problems and rate less severe QoL problems, when compared with those experiencing poorer fitness. Further, those who were experiencing higher fitness levels were also more likely to experience a higher physical QoL, and fewer endorsed and less severe physical problems. Higher fitness levels were also related to improved psychosocial, medical interaction, marital and sexual QoL, however only the relationship between fitness and medical interaction and sexual QoL at PII, reached statistical significance.

**Table 8.9** Relationship between functional capacity (aerobic capacity in ml/FFM/min) and QoL measures of the study group at PI, PII and PIII

<b>Correlations:</b>	Functional capacity	PI (n=6)	PII (n=12)	PIII (n=11)
Total QoL Global	Pearson Correlation	-0.505	-0.641*	-0.685*
	Sig. (2-tailed)	0.385	0.025	0.020
Total QoL Endorsed Problems	Pearson Correlation	-0.281	-0.403	-0.630*
	Sig. (2-tailed)	0.647	0.194	0.038
Total QoL Average Severity	Pearson Correlation	-0.676	-0.708**	-0.273
	Sig. (2-tailed)	0.211	0.010	0.417
Physical QoL Global	Pearson Correlation	-0.762	-0.750**	-0.751**
	Sig. (2-tailed)	0.135	0.005	0.008
Physical QoL Endorsed Problems	Pearson Correlation	-0.384	-0.634*	-0.735*
	Sig. (2-tailed)	0.523	0.027	0.010
Physical QoL Average Severity	Pearson Correlation	-0.861	-0.792**	-0.656*
	Sig. (2-tailed)	0.061	0.002	0.028
Psychosocial QoL Global	Pearson Correlation	-0.176	-0.201	-0.495
	Sig. (2-tailed)	0.778	0.532	0.121
Medical Interaction QoL Global	Pearson Correlation	-0.036	-0.609*	-0.435
	Sig. (2-tailed)	0.954	0.036	0.181
Marital QoL Global	Pearson Correlation	-0.524	-0.484	-0.403
	Sig. (2-tailed)	0.365	0.111	0.219
Sexual QoL Global	Pearson Correlation	-0.666	-0.653*	-0.481
	Sig. (2-tailed)	0.220	0.021	0.134

\*  $p < 0.05$

\*\*  $p < 0.01$

While the results presented in Table 8.10 demonstrate a trend towards a relationship between the level of change experienced in aerobic capacity and the level of change experienced in QoL, the relationship was not statistically significant.

**Table 8.10** Relationship between the level of change in functional capacity (aerobic capacity in ml/FFM/min) and QoL measures between PII and PIII

		The level of change experienced in total QoL between PII and PIII
The level of change experienced in aerobic capacity (ml/FFM/min) between PII and PIII	Pearson Correlation	-0.562
	Sig. (2-tailed)	0.091
	N	10

## 8.4 Discussion

Undergoing a PBST was associated with a negative impact on QoL, together with mean increases in the number of endorsed problems and the average severity of those problems. However, significant improvements were observed in total QoL and a number of QoL domains when patients participated in the 3-month exercise program following treatment. Further, exercising patients demonstrated a significantly improved QoL when compared with pre-transplant ratings, non-exercising transplant patients and patients with cancer who have undergone more conventional treatment regimens. Moreover, fitness and QoL are related, with those experiencing higher fitness levels, also experiencing a superior QoL.

### 8.4.1 Effect of undertaking a PBST on quality of life

Undertaking intensive chemotherapy followed by a PBST had a detrimental impact on total QoL, with adverse changes in the mean physical, psychosocial, medical interaction, and sexual QoL ratings, contributing to this overall QoL effect. With the exception of the sexual QoL score, a mean increase in the number of endorsed problems, as well as a mean increase in the average severity of the problems, were associated with the reduced total QoL and QoL domain ratings.

An impaired physical QoL dimension, in conjunction with a greater number of physical problems endorsed and an elevation in physical problem severity following a transplant, may not seem surprising. Many physiological decrements and their corresponding impact on physical function have been outlined in detail in the previous chapters of this investigation. However, an examination of the change recorded in many of the physical subscales between PI and PII provided further explanation to the mean changes observed in physical QoL. A mean increase in the number of endorsed problems relating to ambulation, activities of daily living, weight loss ( $p < 0.05$ ), recreational activities, difficulty working ( $p < 0.05$ ) and clothing, contributed to the poorer physical QoL rating following the transplant. In contrast, the average number of endorsed problems and average severity for the pain subscale improved by PII, potentially indicating that pain control and relief

throughout the treatment process was effective or that these patients were not experiencing pain. The number of endorsed problems for difficulty working ( $p < 0.05$ ) also improved by PII, however the average severity of the problems was higher ( $p < 0.01$ ). These results indicated that the ability to work at PII may not be an issue for some patients. However, for those who were considering or attempting to work, the severity of the endorsed problems became more pronounced.

Previous studies have also documented the impact of cancer treatment on physical QoL. Adverse physiological changes such as a reduction in cardiovascular and pulmonary function, poorer exercise tolerance and changes in body composition, which in turn lead to an inability to maintain or resume normal daily activities has been reported in breast cancer patients<sup>155, 246</sup>, adolescents with cancer<sup>192</sup>, and BMT patients<sup>11, 105</sup>.

The mean changes observed in psychosocial QoL following the transplant were also supportive of previous findings. The items represented in the psychosocial component of the CARES questionnaire covered topics including body image, psychological distress, cognitive problems, communication and interactive issues, anxiety, worry and work concerns. Although the changes in psychosocial QoL following the PBST were not significant, on average, patients in this investigation rated a lower psychosocial QoL, endorsed a greater number of psychosocial problems and rated the average severity of these problems higher, when compared with pre-transplant reports. Disturbances in body image and self-concept and an elevation in emotional distress have also been reported following breast cancer treatment<sup>246</sup>. Adolescents with cancer have demonstrated depression and altered self-concept and body image perception following treatment<sup>192</sup>. Social, psychological and emotional impairments have been reported following BMT<sup>11, 206, 424</sup>.

The component of the CARES questionnaire that is relevant to medical interaction QoL includes items relating to problems obtaining information from the medical team, difficulty communicating with the medical team and inability to control the medical team. Although the mean global score following the transplant indicated a lower medical interaction QoL, the change was not significant. It was evident during

informal interviews that while some patients maintained an effective relationship with medical staff, others found that certain treatment side effects influenced the ability to communicate with the medical team. For example, fatigue or weakness, or sleeping during times medical staff were present, prevented patients from asking questions regarding cancer issues. Fears associated with the disease or treatment, or simply an inability to understand medical terminology, were other potential factors that influenced communication.

The marital QoL domain relates to the ability to communicate with a partner, the ability to show affection and interact with a partner, and whether the patient is feeling overprotected or neglected by their partner. In this investigative sample the transplant had little effect within the marital QoL domain, indicating that the transplant process was neither advantageous nor disadvantageous to marital relationships. Previous investigations regarding changes to personal relationships with cancer treatment have presented inconsistent results. While a positive effect on relationships has been shown in BMT patients<sup>85</sup>, peer relationship problems and disruption to family relationships have been reported in adolescents with cancer<sup>192</sup> and women with breast cancer<sup>155</sup>.

The sexual domain relates to sexual interest and sexual dysfunction issues. Sexual problems may arise as a result of fatigue, poor body image, and muscular weakness<sup>50</sup>. Economic worries, changes in anatomy and physiology due to surgery and/or treatment, and other psychological concerns are other factors that may contribute to sexual problems. Although changes were not significant, the mean adverse change observed in sexual QoL following the PBST was supportive of previous findings in both breast cancer<sup>155</sup> and BMT patients<sup>13</sup>.

Finally, the PBST patients experienced similar total QoL, and psychosocial, sexual, medical interaction and marital QoL, to those who had undertaken more conventional treatment regimens for cancer<sup>76</sup>. However, physical QoL was poorer when compared with normative cancer data, indicating that intensive treatment imposes a greater impact on physical health, when compared with more conventional treatment. This finding is in contrast to previous physiological results presented in Chapter 5, which demonstrated that the aerobic capacity (which is a common

measure of functional capacity) of the PBST patients at PII, was similar to the initial exercise capacity of cancer patients<sup>3</sup> who have undergone conventional treatment for breast cancer. One potential reason for the confounding results is that the QoL data were compared with normative data derived from a range of cancer patients, while the physiological data were compared with data derived from breast cancer patients only.

When comparing this study sample to the normative cancer data derived from over 1000 patients, it is also important to compare group characteristics. As is similar to the investigative sample, the normative sample includes patients who have been diagnosed with a variety of malignancies and who have undergone a variety of treatment regimes. Additionally, the majority of the normative group has at least completed secondary education and is married. The mean and range for age is 64.05 years (21-99 years) and 56.83 years (21-87 years) for the male and female patients, respectively. Therefore, the normative cancer data has been derived from a slightly older population. A potential implication of the difference in age between the two groups, could be a poorer QoL in the older group. However, as is evident from the results of the QoL comparisons, this investigative sample experienced a similar QoL and QoL domains to the normative group, with the exception of physical QoL. Consequently, it could be suggested that treatment intensity may have a greater impact on QoL, when compared with age.

In summary, evidence demonstrates that cancer treatment is associated with a reduced QoL. Consequently, it is becoming more important to investigate intervention strategies that could prevent, minimise or reverse the adverse QoL changes experienced by the cancer patient.

#### **8.4.2 Effect of a 3-month recovery period on quality of life**

“The ability to maintain or resume one’s pattern of life activities is an undisputed aspect of quality of life”<sup>226</sup>. When resumption of normal roles is prevented by impaired functional capacity, the patient and family are confronted with demands of illness and disability. The psychological reactions to disease and treatment can be intensified as a consequence of dependence on others, or fear of being dependent on

others for basic needs. Interventions which can influence the ability and capacity to perform daily activities, in turn, influence QoL<sup>430</sup>. The physiological and psychological health benefits derived through participation in regular exercise, by healthy subjects and certain diseased populations, have been extensively reported throughout the literature. However, research to date regarding the role of exercise in the cancer domain has been relatively scarce.

Both non-exercising and exercising PBST patients demonstrated similar changes across the testing phases, with regards to total QoL, and individual changes of the subjects were representative of the mean group changes reported. Three-months post-transplant, QoL ratings had significantly improved for both the control and exercising subjects. However, the exercising subjects also demonstrated significant improvements in the number of endorsed problems and the average severity of these problems. Additionally, the EG participants were able to achieve a higher QoL, fewer number of endorsed problems and less severe QoL problems at PIII, when compared with pre-transplant. Moreover, by PIII, the exercising patients reported a higher QoL when compared with non-exercising PBST patients, and patients who have undergone conventional treatment regimes. Taken together, these results indicate that although improvements in QoL can be attained by 3-months following treatment, QoL could be further improved through participation in an exercise program.

A review performed on 24 studies regarding exercise, QoL and cancer, found that participation in physical exercise consistently demonstrated a positive effect on QoL following cancer diagnosis<sup>77</sup>. Others have reported that exercising breast cancer patients experience an enhanced life satisfaction, and that the improvement observed in QoL is proportional to the amount of exercise undertaken<sup>291</sup>.

Greater insight regarding the role of exercise on QoL, can be attained by analysing changes to the specific QoL domains during the recovery period.

#### **8.4.2.1 Physical QoL**

Exercising patients demonstrated significant improvements in physical QoL, and the number of endorsed physical problems and the average severity of those problems, by 3-months post-transplant. Although the non-exercising patients showed mean improvements in physical QoL, the changes were not significant. Furthermore, physical QoL at PIII was higher than at PI for the EG, indicating that patients maintained the ability to return to higher than pre-transplant physical QoL within a period as short as 3-months. Following the intervention program, exercising patients also scored a significantly higher physical QoL when compared with the CG and normative cancer group, and reported significantly fewer and less severe physical problems, when compared with the CG.

Variations in the physical subscales can explain the changes observed in the physical domain for the CG and EG. While the general trend for the CG following a transplant was a reduction in the number of endorsed problems and average severity of these problems by PIII, only the changes detected for the average severity of the problems related to difficulty working were of significance. Importantly, although the average severity of the problems for 'difficulty working' significantly decreased, the number of endorsed problems during the same period, increased. In comparison, the exercising patients displayed numerous significant and beneficial changes between immediately post-transplant and 3-months post-transplant. These were within the subscales of ambulation, activities of daily living, weight loss, recreational activities, difficulty working and clothing. The exercising group endorsed fewer problems and rated the severity of the problems lower for all of the physical subscales at PIII, when compared with the CG. Differences were significant with the exception of the number of endorsed problems relating to ambulation, pain and difficulty working, and the average severity of problems within the subscales of activities of daily living and weight loss. Finally, following 3-months participation in a regular aerobic and resistance training program, exercising patients demonstrated significantly fewer and less severe endorsed problems relating to ambulation, recreational activities, and difficulty working, when compared with pre-transplant levels. Similar physical benefits have also been shown in exercising patients with

breast cancer<sup>247, 445</sup>, exercising adolescents with cancer<sup>192</sup> and exercising BMT patients<sup>104</sup>.

With regard to the pain subscale, while the mean number of endorsed problems relating to pain gradually decreased across the phases for the non-exercising subjects, the mean average severity increased. In contrast, both the mean number and severity of pain problems decreased gradually across the 3 testing phases for the exercising patients. By 3-months post-transplant, exercising PBST patients reported significantly less severe pain problems in comparison with the control group. These results are supportive of others who have also found that exercising BMT patients reported less severe pain<sup>102</sup>.

#### **8.4.2.2 Psychosocial QoL**

Little variation occurred in psychosocial QoL of non-exercising patients following a transplant. In comparison, those who exercised regularly demonstrated significant improvements in the global, number of endorsed problems and average severity score at PIII, when compared with immediately post-transplant. By 3-months post-transplant, exercising PBST patients were able to achieve an improved psychosocial rating, and significantly fewer and less severe endorsed problems, when compared with pre-transplant levels and with non-exercising patients. Comparisons with normative cancer data also demonstrate that the EG experienced a significantly higher psychosocial QoL. Contributing to this enhanced psychosocial QoL for the exercising patients were reductions in psychological distress, worry, anxiety, body image concerns, work concerns, cognitive problems, difficulty communicating with friends and relatives and difficulty interacting with friends and relatives.

A review performed on 24 studies in the area of exercise, cancer, and QoL found that exercise was shown to induce a positive effect on psychological, emotional and social well-being<sup>77</sup>. The findings of this investigation support previous work that has reported a reduction in depression<sup>226, 246</sup>, anxiety<sup>226</sup> and total mood disturbance<sup>226</sup>, and enhanced self esteem and confidence<sup>246, 257, 369</sup> in exercising breast cancer patients. Additionally, an enhanced self-concept and improvement in family and

friend relationships have been previously reported in exercising adolescents with cancer<sup>192</sup>.

Results involving women with breast cancer indicated that while exercise participants demonstrated an enhanced mood status, non-exercising subjects displayed a worsening of mood states<sup>226</sup>. Others comparing exercising patients being treated with radiation for breast cancer, to non-exercising patients undertaking the same treatment regimen, noted that while factors such as anxiety and depression were common for both groups, the non-exercising patients experienced greater symptom intensity<sup>247</sup>.

Findings derived from previous investigations of BMT patients are also similar to those presented here. An improvement in self-confidence and depressed mood states, and an improved mental status, has been demonstrated in exercising BMT patients<sup>102</sup> and exercising autologous PBST<sup>105</sup>. Additionally, although psychological distress scores including depression, fear, anger/hostility, interpersonal sensitivity and phobic anxiety, were reduced for the exercising autologous PBST subjects, the control group showed no improvement in mood state. Findings reported by others<sup>12</sup> have linked depressed mood, functional QoL and mental adjustment with survival in BMT patients and other patient groups. These results highlight the importance for intervention programs to effectively influence these factors.

#### **8.4.2.3 Medical interaction QoL**

Little change was detected for medical interaction QoL across the phases for both exercising and non-exercising participants. While comparisons between the global, endorsed problems and average severity rating for the CG and EG at PIII, indicated that participation in an exercise program had little impact on this QoL domain, comparisons with normative cancer data suggest otherwise. By 3-months post-transplant, exercising subjects reported significantly higher medical interaction global scores in comparison to normative cancer data, while the differences between the CG and normative data were not significant. Classifying the area of 'medical interaction' as a component of QoL is unique to the CARES questionnaire. Consequently, a paucity of data exists regarding changes in patient's ability to

control or communicate with the medical team across the cancer continuum. Nevertheless, the results of this investigation indicate an improved medical interaction QoL with participation in an exercise program. It is possible that the physical or psychosocial benefits sustained through exercise participation - such as enhanced energy, reduced fatigue or weakness, enhanced self-confidence and/or an improved ability to communicate - could lead to an improved ability to interact with the medical team.

#### **8.4.2.4 Marital QoL**

No change was observed across the phases for either non-exercising or exercising patients in marital QoL. By 3-months post-transplant, the global, endorsed problem and average severity ratings for both the CG and EG were similar, indicating that the exercise program had little influence over marital issues relating to communication, affection and interaction with a significant other.

#### **8.4.2.5 Sexual QoL**

Similar changes were observed across the phases for both non-exercising and exercising patients with regards to sexual QoL, and the number of endorsed problems and average severity of the problems, relating to the sexual domain. It was found that the transplant process was associated with adverse changes, and the 3-month recovery period was associated with improvements. While the positive changes observed during the recovery period were significant for both the CG and EG, the improvements in the number of endorsed problems were only significant for the exercising patients. Little difference existed between the global scores reported at PIII for exercising and non-exercising patients, and normative cancer data. These results indicate that exercise participation has little influence over changes in this domain, and therefore factors other than physical changes, body image perception, anxiety and depression, must influence sexual QoL.

In summary, mean QoL, endorsed problems and average severity scores indicated that the exercising patients reported higher total QoL and QoL domains, when compared with non-exercising patients, 3-months post-treatment. These differences

were significant for total QoL, and physical and psychosocial QoL. The results therefore suggest that a physical intervention program has the potential to induce more than just physiological changes.

### 8.4.3 Relationship between functional capacity and quality of life

While impairment in physical fitness is a substantial contributor to reduced QoL in cancer patients<sup>105</sup>, this investigation has demonstrated that functional capacity is associated with QoL. Correlations performed on QoL data with aerobic capacity data (details described in Chapter 5) indicated that those who were experiencing a higher level of fitness were more likely to also experience a higher QoL ( $p < 0.05$ ), and fewer ( $p < 0.05$ ) and less severe ( $p < 0.01$ ) QoL problems. Not surprisingly, those who demonstrated higher fitness levels also demonstrated a more favourable physical QoL ( $p > 0.01$ ), and fewer ( $p < 0.05$ ) and less severe physical problems ( $p < 0.01$ ). Although the relationship between the level of change experienced in aerobic capacity and QoL, between PII and PIII, was not significant, the results suggest that those subjects who showed the greatest improvement in aerobic fitness following treatment also showed the greatest improvement in QoL.

Moreover, it has been previously suggested that participation in a regular exercise intervention program, may simultaneously influence many dimensions of QoL, or alternatively, it may directly influence one dimension, which in turn has a 'domino effect amongst other wellness domains'<sup>445</sup>. The results of this investigation support this statement as physical fitness was also found to be highly correlated with medical interaction ( $p < 0.05$ ) and sexual QoL ( $p < 0.05$ ), and correlated, but not significantly, with psychosocial and marital QoL. It should be noted that the significant correlations were found during the analysis of PII and/or PIII data, where the number of data points were maximised ( $n = 12$  and  $13$ , respectively). Although a relationship was also detected between QoL and certain QoL dimensions, and aerobic capacity at PI, only 6 six data points were available for the analysis, and in turn, the ability to detect a significant relationship between the variables was reduced.

While the functional capacity as measured by aerobic capacity is linked with QoL, it has also been found that functional QoL is associated with post-BMT survival<sup>12</sup>.

Those who experience a lower functional QoL are associated with poorer post-BMT survival and those who demonstrate a higher functional QoL evidence a trend toward longer survival. These results indicate that physical fitness has the potential to influence both the quantity and quality of life, and highlight both the importance of functional well-being in cancer patients, and the potential inadequacy of QoL interventions that fail to address physical concerns<sup>77</sup>.

## **8.5 Conclusion**

Significant adverse changes in QoL were associated with undergoing high-intensity chemotherapy treatment followed by a PBST. While total QoL significantly improved over time without an intervention program, further improvements were attained through participation in the aerobic and resistance training exercise program. This was evident by the exercising patients rating a significantly higher QoL when compared with non-exercising patients. Moreover, unlike the non-exercising patients, the exercising patients attained a higher QoL within 3-months post-transplant, when compared with pre-transplant ratings.

Further, improvements in functional capacity were significantly related to physical QoL. However, the effect of the intervention was not just limited to better physiological function. Indeed, the improvements in physical status positively influenced numerous factors relevant to psychosocial, marital, medical interaction, and sexual QoL. In summary, the degree of functional capacity improvements derived through exercise participation was highly related to improvements in total QoL and certain QoL domains. That is, patients experiencing a higher aerobic capacity were more likely to experience a higher QoL than those patients less physically fit. Finally, these results provide crucial evidence demonstrating the need for patients to participate in a physical intervention program following cancer treatment.

# CHAPTER NINE

## SUMMARY AND CONCLUSIONS

*“It (the exercise intervention program) was certainly a very positive experience in a year that was very difficult health-wise. I guess we were focused on doing something of great benefit to ourselves – to be in control of our bodies, of our lives, again, and this is really important.”*  
*EG participant (2000)*

## 9. Summary and Conclusions

---

### 9.0 Summary

As medical technology has advanced, outcomes have improved for many malignancies, and thus survival rates (defined as a relative combined 5-year statistic) of those diagnosed with cancer are progressively increasing each year. Survival rates for those undertaking a PBST have now reached approximately 50-80%, depending on the cancer diagnosis<sup>166</sup>. Given this improved outcome, it is essential to investigate the impact of cancer and its associated treatment, as well as addressing research issues such as facilitating recovery post-treatment and improving quality of life for cancer patients.

This investigation was designed to assess changes in functional capacity and QoL following a PBST and participation in a 3-month aerobic and strength training program. Factors that directly or indirectly influence functional capacity were measured and included body composition, aerobic capacity, muscular strength, immunological status and function, and bone turnover. Outlined below are the primary objectives that were originally defined in Chapter one, followed by the findings of the investigation.

Objective 1:

To investigate changes between pre- and post-transplant measures of functional capacity and quality of life.

*Conclusions:*

- Functional capacity measures of body composition, aerobic capacity, muscular strength, immunological status and function, and bone turnover showed adverse changes following the PBST.
- Undertaking a PBST was associated with a reduction in total QoL.

Significant losses in body weight, body mass index, and most importantly, lean tissue were observed following the transplant. These negative changes to body

composition occurred in the presence of decreasing energy expenditure levels indicating the presence of an energy imbalance. Adverse changes to muscular strength, in particular upper body strength, were also evident, and were a likely consequence of the reduction in lean tissue measured during the same period. Aerobic capacity also showed a mean decline. Although the change between pre- (PI) and post-transplant (PII) was not statistically significant, it could be considered clinically relevant, since aerobic capacity at PII was considered significantly lower than age- and sex-matched healthy controls.

The measurement of certain immunological parameters at PI indicated that the patients were already immunocompromised prior to undergoing the transplant. While the absolute WBC count, percentages of CD3+, CD4+ and CD8+ cells and the CD4+/CD8+ ratio were considered normal at PI, the absolute counts of lymphocytes and T cell subsets, and T cell function, were considered below normal. The objective of a PBST is to destroy rapidly dividing cells, which include both malignant cells and cells within the bone marrow. Therefore, as was expected, further adverse changes were observed for T cell function, and total leucocyte, lymphocyte, CD3+, CD4+, and CD8+ counts, and the helper/suppressor ratio, following the transplant.

These findings and additional adverse physiological effects may influence functional capacity and QoL, both in the short- and longer-term. For example, following the transplant the mean bone resorption and formation activity was elevated, indicating a rise in bone turnover. Bone resorption was significantly increased suggesting that an uncoupling of osteoblastic and osteoclastic function occurred post-transplant. Consequently the risk of bone loss in PBST patients was elevated following the transplant, which could influence the longer-term risk of osteoporosis unless arrested.

It was also shown that undergoing a PBST was associated with negative changes to total QoL, as measured by the CARES QoL tool. Mean changes in the number of identified problems, and average severity of the problems in physical, psychosocial, medical interaction, marital and sexual QoL, contributed to the overall change observed in total QoL. These results, in conjunction with increasing survival rates, highlight the need for effective intervention strategies to assist patients in achieving

their optimal level of physical functioning and QoL following treatment. Further, there is a definitive need to 'bridge the gap' between treatment cessation and returning to a 'normal life'.

Exercise has been shown to provide physical and psychological benefits during the rehabilitation process of patients with chronic diseases including cardiovascular disease, rheumatic disease, diabetes mellitus, and renal disease. Although evidence is limited and predominantly relates to patients with breast cancer, exercise intervention programs during or following cancer treatment have been associated with positive changes. This investigation was designed to extend our knowledge in this area and aimed to assess the role of exercise in the recovery of PBST patients.

To this end, following the transplant, patients were divided into an exercise intervention group or a stretching/control group for a period of 3-months. Exercising patients participated in an aerobic and strength program, 3 times/week, while those in the control group performed a flexibility/stretching regime, 3 times/week. The second primary objective as defined in Chapter 1, in conjunction with the results obtained through this investigative design, are outlined below.

Objective 2:

To investigate the role of a three-month duration, moderate intensity and mixed type exercise program in the recovery of functional capacity and quality of life, post-PBST.

*Conclusions:*

- Recovery of body composition, aerobic capacity, muscular strength and QoL was faster for the exercising patients, when compared with the non-exercising patients.
- Participation in the exercise program failed to influence recovery rates of immunological factors.
- While the results observed for changes in bone turnover were more favourable by three-months post-transplant for the exercising patients, in comparison with the non-exercising patients, it would be inappropriate to relate these preliminary results with improved skeletal status.

- Exercising patients reported higher total, physical and psychosocial QoL ratings when compared with non-exercising patients by 3-months post-transplant.

Participating in a regular progressive physical activity regimen led to a significant increase in energy expenditure, whereby total energy expenditure at 3-months post-transplant was significantly higher than both immediately post-transplant and pre-transplant levels. Exercising patients also demonstrated significant increases in lean tissue to levels that were higher than at pre-transplant. Body fat levels continued to reduce during the 3-month exercise period, and were significantly lower at PIII when compared with post-transplant levels. These changes in energy expenditure and body composition were accompanied by other important functional changes. Both fitness and muscular strength significantly improved by 3-months post-transplant, to levels that were clinically and/or statistically higher than those recorded pre-transplant. Improvements in function were also detected by the use of the QoL tool with exercising patients rating their physical QoL at PIII significantly higher than their pre- and post-transplant ratings.

In comparison, non-exercising patients failed to demonstrate the same level of improvement throughout the 3-month period. While some measures demonstrated a mean improvement, others continued to show a mean decline during the 3-months post-transplant. Body composition was stable during this period, with little change being detected in body fat and lean tissue. However, of clinical and functional significance was the inability of this group to regain lean tissue lost during the transplant process. The maintenance of lower lean tissue mass was also reflected in strength results. While changes in strength measures between PII and PIII were not significant, the group mean for lower-body and hand-grip strength continued to deteriorate during the 3-months following the transplant. Finally, both aerobic capacity and physical QoL were other measures that failed to improve throughout the 3-month recovery period. The findings from the control group indicated that more than 3-months might be required to recover pre-transplant function when regular exercise is not performed following the transplant. Additionally, patients who do not participate in regular exercise following treatment are at risk of experiencing further functional declines.

Participation in exercise had no impact on immunological changes across the testing phases. White blood cell and CD8+ cell counts returned to normal within 3-months post-transplant, however the lymphocyte, CD3+, and CD4+ cell counts demonstrated a delayed recovery for both exercising and non-exercising patients. Although participation in the exercise program had no influence on immune cell recovery following a PBST, importantly immune recovery was not adversely effected, demonstrating that exercise participation was of no detriment to immune status and function for these patients.

Three-months post-transplant, the bone resorption activity of the exercising patients showed a significant decline. The changes observed in bone turnover between PII and PIII indicated an uncoupling of formation and resorption activity, favouring formation. In contrast, the control group demonstrated a mean reduction for both resorption and formation activity by PIII. During this same period, the non-exercising patients experienced mean resorption activity above, and mean formation activity below, pre-treatment levels. Although preliminary, the results suggest that participation in an aerobic and resistance training program may have a favourable influence on bone metabolism. In turn, the development of longer-term skeletal conditions such as osteoporosis could be prevented through participation in an intervention such as an aerobic and strength training program.

A three-month recovery period following a PBST is associated with significant improvements in total QoL, regardless of whether patients perform regular physical activity. However, exercising patients were experiencing a higher QoL when compared with the control participants at PIII, with the results suggesting that further improvements in QoL can be sustained through regular exercise. Participation in an aerobic and resistance training program was also associated with significant improvements in the number of identified problems relating to total QoL and physical QoL, the average severity of these problems, and physical and psychosocial QoL. The exercise participants also demonstrated higher QoL ratings when compared with pre-transplant ratings, and ratings recorded by patients who had undergone more conventional treatment regimens.

In summary, exercise participation has the potential to reverse detrimental functional and QoL effects experienced as a result of cancer and its associated treatment, without initiating any adverse consequences. The third objective of this investigation, was to determine whether functional capacity is related to QoL.

Objective 3:

To investigate the relationship between functional capacity and quality of life of PBST patients.

*Conclusions:*

- The effects of physical activity were not limited to better physiological function. Functional capacity (as measured by aerobic capacity) was significantly related to total QoL and physical, psychosocial, marital, medical interaction, and sexual QoL. Those that experience a higher aerobic capacity were more likely to also experience a higher QoL.

The experience and knowledge gained during the design and implementation of this investigation led to the attainment of the final general objective.

Objective 4:

To demonstrate that patients with cancer who are required to undergo intensive cancer treatment regimens such as PBST, are still able to participate and tolerate a planned regular exercise program.

*Conclusions:*

The intervention program highlighted that:

- PBST patients can safely participate in a regular exercise program of moderate intensity and mixed type, without any adverse consequences.
- PBST patients can tolerate a VO<sub>2</sub> max test and 15RM strength test.
- The overload utilised in this investigation was appropriate for these patients as it ensured progression without inducing adverse effects such as undue fatigue.
- PBST patients should not be restricted to 'low' exercise intensities.

- An exercising frequency of 3 times/week of up to 40 minutes duration for aerobic exercise, and twice/week of up to 6 exercises for strength training is sufficient to induce a significant training effect.
- In summary, PBST patients can participate in a regular exercise program safely and can tolerate overload and progression in both the aerobic and strength training components.

The current research project used existing guidelines for exercise prescription and contraindications to exercise for cancer patients<sup>429</sup> as a basis for the development of the intervention protocol implemented. However, in the conduct of this investigation and after consultation with both patients and medical supervisors, it became obvious that in some areas the current guidelines were inappropriate. For example, according to exercise guidelines<sup>426</sup>, platelet counts should be greater than 50 000/mm<sup>3</sup>, haemoglobin more than 10g/dL, WBC count greater than 3 000/mm<sup>3</sup> and absolute granulocyte count higher than 2 500/mm<sup>3</sup>. However, only one out of six exercising patients progressed through the entire intervention period with all blood counts above these recommended levels. Haemoglobin, platelet and WBC counts were below 'optimal' in 34%, 17% and 67% of patients, respectively, at some stage during the intervention period. The lowest counts recorded during the intervention period were 77g/L for haemoglobin, 26 x 10<sup>3</sup>/uL for platelets, and 0.9 x 10<sup>3</sup>/uL for WBC. While counts were outside current guidelines, they were above the minimum requirements set for a previous investigation involving BMT patients<sup>104</sup>, where platelets counts needed to be greater than 20 x 10<sup>9</sup>/L and leucocyte counts above 1.5 x 10<sup>9</sup>/L.

The nature of the program, including the prescriptive characteristics of type, intensity, duration and frequency of exercise, can determine the extent of the benefits attained<sup>3</sup>. Aerobic exercise such as walking, cycling and swimming, and dynamic lifting on weight machines have been recommended for cancer patients<sup>3</sup>. Intensity guidelines have recommended that patients should work within 50-85% VO<sub>2</sub> max or 65-90% HRmax<sup>3</sup>. Additionally, it has been suggested that for those who are deconditioned following diagnosis and treatment, maintaining a HR intensity of 60% HRmax is sufficient<sup>425</sup>. Caution is required when prescribing unsupervised programs and lower HR ranges of 40-65% of the estimated HRR<sup>426</sup>, or a working intensity corresponding to 60% VO<sub>2</sub> max<sup>161</sup> should be utilised.

While various protocols have been employed, the majority of studies have involved women during or after treatment with breast cancer, and have implemented aerobic only programs that work within the exercise guidelines recommended above. Only recently have exercise intervention programs been implemented among BMT or PBST patients during<sup>102, 105</sup> and after treatment<sup>101, 104</sup>. These exercise programs were aerobic in nature and worked within the ACSM guidelines. The intervention assessed in this investigation was unique, as it involved a combination of aerobic and resistance exercise, for a duration of 12 weeks. While 12-week duration programs have been implemented in breast cancer populations, no other study could be identified that followed exercising PBST or BMT patients for this length of time. Furthermore, the exercise program of this investigation required patients to work at an initial intensity of 70% HRmax, which progressively increased over time to 90% HRmax. Exercise duration was initially 20 minutes, but progressed to no less than 40 minutes by the end of the 12 weeks. The volume of work performed during the exercise sessions by the PBST patients is also unique to this investigation.

### **9.0.1 Research or clinical implications of working with patients with cancer**

Inability to recruit adequate numbers of patients is a limitation in cancer research and has the potential to influence the success of a program. During the subject recruitment phase, it became evident that referral and encouragement by medical practitioners was crucial in attaining subjects. The importance of a doctor's belief in the benefit of a drug or in this instance an experimental program, to patient acceptance and/or participation has been discussed throughout the literature<sup>42</sup>. Willingness to participate during cancer treatment and its side effects, is no small endeavour for the patient. More specifically, recruiting patients prior to transplant is often at a time when patients are feeling depressed and have little energy to perform daily activities. Associated with these recruitment limitations is the influence of family and medical staff and their common recommendation that patients should 'take it easy' and 'get plenty of rest' during and following treatment. While this investigation provides evidence that an exercise program should form a primary component of cancer rehabilitation, it also highlights the need for medical practitioners' support.

Another important consideration for the success of an intervention program is program acceptance and adherence. Previous exercise intervention programs performed with BMT patients have reported a 90% acceptance rate<sup>101</sup> and have suggested that patients perceive their 'active' role in the rehabilitation process, compared with their previously 'passive' role in the diagnostic procedure and treatment process, as a 'welcomed change'. The program acceptance and adherence rate of this investigation supports these findings. All patients within the exercise group adhered to the program, working at above the minimum intensity and duration of each exercise session. Additionally, only 2 patients failed to attend 1 week of the 12-week program, due to illness. Comments regarding 'ownership' of the program, or 'personal control', were commonly stated by exercising patients during informal interviews, and it was felt that these feelings may have contributed to the program acceptance and adherence rate attained. The benefits achieved through exercise influence the ability to perform normal daily activities, and these benefits are often realised by the patient relatively quickly. This research indicates that patients can achieve 'normal' function within 3 months, and it is likely that these rapid improvements also contributed to the excellent adherence rates attained. Therefore it seems evident that, although difficulties are present during the recruitment phase, once patients have agreed to participate, program adherence is not problematic, at least for a 3-month program.

The small number of subjects in this investigation reflects the recruitment difficulties faced when dealing with patients with cancer. The recruitment problems experienced are not unique to this investigation, and small sample sizes are not uncommon in cancer research. Recently, a group of Canadian researchers<sup>80</sup> recruited from a major cancer hospital for 14 months, and were only able to initially enrol 39 patients. The recruitment of the 12 subjects for this investigation occurred over a period of 15 months. Consequently, a primary limitation to this study, and many other studies investigating 'exercise and cancer' is sample size. This limitation highlights the importance of further research within the area that both replicates and extends current studies. Nevertheless, while the relatively small number of subjects investigated could be perceived as a potential study limitation, the statistical power was sufficient to detect many of the changes observed as statistically significant (at

two-tailed, alpha of 0.05). In addition, the assessment of individual change made throughout the thesis demonstrated that all subjects displayed a similar trend of change and magnitude of change. As such, the group mean change was representative of individual change. The results attained also supported results previously found in investigations using larger sample sizes. In turn, the similarities between study findings add credence to the validity of the results presented here.

Initially, patients were to be randomly divided into two groups with age stratification, as they were recruited into the study. Unfortunately, the ability to attain matched control and experimental groups through randomisation was limited as a consequence of the slow recruitment rate, and thus low subject numbers. Therefore, the two groups were matched as closely as possible, taking into account all variables including cancer diagnosis, age, sex, treatment regimen to be undertaken, previous and current exercise habits, marriage status, weight and living distance from the hospital and exercise centre. Chapter 3 provides detailed information regarding group demographics and demonstrates that while the groups were not randomly created, they were closely matched. The ability to achieve closely matched groups further supports the findings that the positive responses may be attributed to the intervention program.

Although limitations exist when working with patients with cancer, the available research has provided support for the role of exercise in cancer rehabilitation. Future research is, however, required to extend this current body of knowledge.

### **9.0.2 Potential for future research**

In conformity with good research models, the results of this investigation highlighted areas in exercise and cancer which require further research. As a consequence of the nature of the intervention program implemented in this investigation, it was not possible to determine the contribution of the strength or aerobic program towards the functional and QoL changes measured. The inclusion of a greater number of experimental groups performing various exercise protocols, would provide greater insight into the benefit of specific types of exercise.

Additionally, this investigation evaluated the role of exercise following treatment for cancer and made no attempt to determine the role of exercise during the diagnosis to treatment period, or during the treatment period itself. Research demonstrates that participation in physical activity for cancer patients declines from point of cancer diagnosis<sup>80</sup> and remains low throughout the treatment process, and following treatment. Therefore, the risk of decreased functional capacity elevates at the point of diagnosis as a consequence of the disease process itself, as well as a reduction in physical activity. Once treatment is initiated, this risk further escalates. Future research should investigate the optimum time throughout the cancer continuum that initiation of a physical intervention program will be of greatest benefit. It seems likely that those who exercise from point of diagnosis through to complete recovery, will maintain a higher functional capacity and thus QoL throughout the entire cancer continuum.

Prior to this study, research has predominantly assessed functional capacity via the measurement of aerobic capacity. While this may be appropriate, future research should consider a greater range of physiological measures, which may influence function in both the short- and longer-term. Additionally, future research should begin to test the limits of exercise prescription guidelines available for patients with cancer. The list of questions provided below highlights potential areas in exercise prescription, for future research:

- What are the boundaries of exercise prescription for cancer patients? That is:
  - While an exercising intensity equivalent to 60% HRmax has the potential to lead to benefits in deconditioned patients, can these patients work harder without inducing adverse effects?
  - Is it necessary for patients to wait an extra day following an ‘unwell’ day before they return to their exercise program? If they are feeling ‘well’, why is it necessary to wait an additional day?
  - Does an elevated pulse at 10 minutes post-exercise really indicate a need for reducing the exercise intensity of the following session, or is it an indication of an ineffective cool-down, or is it simply a side effect caused by certain medications?

- Is it necessary to reduce exercising intensities during unsupervised sessions – what are the potential risks to the patient?
- What are the lower limits for intensity, duration and frequency that are required to ensure benefits are sustained?
  
- Do greater duration, intensity, and frequency equate with greater benefits, or do benefits begin to plateau once a certain level is reached?
- Do interval, discontinuous, or ratio work provide the same benefits as continuous work?
  
- Do the type and location of the exercise influence the potential benefits? That is, is walking better than cycling, are group sessions better than individual sessions?

Finally, the positive relationship between physical function and QoL in cancer patients has recently been recognised and demonstrates that an exercise program should be considered a primary component of rehabilitation. However, it is important to remember that exercise is just one component of cancer rehabilitation and should be used to complement other components rather than be used as an alternative strategy. In order to determine the level of emphasis that should be placed on exercise and other components of cancer rehabilitation programs, comparative studies examining the results of various intervention strategies are required. This would ensure that the relative merits of various interventions for a given outcome are realised. Further, these types of studies could also be used to assess whether QoL benefits attained with a combination of intervention strategies are greater than with any particular component alone.

## 9.1 Conclusion

Cancer diagnosis and treatment are associated with side effects that adversely influence function, the ability to perform daily tasks and QoL. Diagnosis and treatment of cancer have also been associated with a reduction in physical activity<sup>78</sup>. Interestingly and importantly, it has been estimated that at least one third of the functional decline observed in cancer patients, can be attributed to hypokinetic conditions that develop as a result of prolonged inactivity<sup>227</sup>. Yet common advice still being given to cancer patients is to ‘go home and take it easy’, or ‘get plenty of rest’. Unfortunately, the creation of a self-perpetuating condition of ‘diminished activity, continued loss of physical function, easy fatigability when attempting daily tasks, followed by a further reduction in activity’, is not uncommon in cancer patients<sup>105</sup>. This progressive physical debilitation fosters a sense of disability, and leads to negative changes in QoL and many QoL dimensions.

The results of this investigation demonstrated that diminished physical activity throughout the cancer continuum and, more specifically, continued diminished activity following treatment, are not inevitable consequences of cancer and treatment. Participation in exercise can reverse the documented adverse cycle of reduced activity and function, and easy fatigability. This investigation demonstrated that exercising patients experienced a faster recovery of lean tissue, aerobic capacity, muscular strength and QoL, when compared with non-exercising patients. Not only were recovery rates faster for a number of physiological variables, but by 3-months post-transplant, exercising patients were experiencing significantly improved peak ventilation, lower-body strength, and QoL when compared with the non-exercising patients. The exercising patients also experienced more favourable percent body fat, lean tissue mass, aerobic capacity, hand-grip strength, and upper-body strength when compared with the non-exercising patients. Moreover, by 3-months post-treatment, exercising patients had improved body composition, aerobic capacity, peak ventilation, body strength and bone turnover when compared with pre-transplant measures. Finally, the mean aerobic capacity for the exercising group was also higher than the mean age- and sex-matched healthy controls. Therefore, although statistics illustrate that 40% of BMT patients require 12 months to regain pre-treatment fitness levels<sup>105</sup>, the results of this investigation demonstrated that patients

maintain the capacity to return to higher than pre-treatment function, in as little as 3 months following treatment.

The exercise intervention program implemented within this investigation consisted of a 3-month combined aerobic and resistance training program. Despite the exercise prescribed being of sufficient magnitude to induce positive changes in certain physiological variables, the type or length of the program administered, had no effect on the recovery of immunological variables. However, although the program did not facilitate immune cell recovery, neither was it hindered. Changes observed in bone turnover, the physiological measures that may influence function and QoL in the longer-term, indicated that participation in the aerobic and resistance training program exerted a favourable influence on bone metabolism through the uncoupling of bone turnover, which favoured bone formation. However, more work is required in the area before these conclusions are definitive.

The positive relationship between functional capacity and QoL was also evident from the results of this investigation. That is, those patients experiencing a higher aerobic capacity were more likely to experience a higher total QoL and higher QoL domains, than those patients less physically fit. Therefore, including wellness-oriented interventions such as physical exercise into the care plans of patients may facilitate a more comprehensive enhancement of the physical, functional, psychological, social and spiritual dimensions of QoL.

In summary, more than 3 months is required for patients to return to pre-transplant function when exercise is not integrated into their care plan post-treatment. Additionally, failure to participate in physical activity following treatment could potentially lead to a further deterioration of function. Participation in exercise following cancer treatment facilitates the recovery of numerous physiological variables, which in turn influences functional capacity and QoL. This investigation provides evidence demonstrating that participation in an exercise program can 'bridge the gap' between treatment cessation, and returning to a 'normal' lifestyle.

# **APPENDICES**

# **Appendix I**

## **Queensland University of Technology ethics approval**



UNIVERSITY RESEARCH ETHICS COMMITTEE

Miss Sandra Hayes  
School of Human Movement Studies  
QUT Kelvin Grove

26 February, 1998

Dear Miss Hayes

I wish to advise that the University Research Ethics Committee has granted ethical approval for the human experimentation proposed in the project "The role of exercise in enhancing functional capacity and quality of life, in the rehabilitation phase of patients who have undergone an autologous blood stem cell transplant (APBST)" (Ref No QUT 1349H). This approval is subject to:

- the informed consent package being revised (as the Committee felt that this was overly long and was not written in lay terms);
- a qualified physician being present to monitor the ECG; and
- an assurance that all body tissues/fluids will be handled in accordance with normal medical/hygiene standards.

Please provide me with the revisions/additional information outlined above by 10 March 1998. Failure to submit this information by the date specified will result in withdrawal of approval for the project.

This approval is valid for the duration of the project or three years, whichever is earlier, commencing from 1 April 1998.

Please note the following conditions of approval:

- any departure from the protocol detailed in your application must be reported immediately to the Committee;
- you are required to advise the Secretary if any complaints are made, or expressions of concern raised, in relation to the project;
- you are required to report on the progress of the approved project at least annually, or at intervals determined by the Committee. The Committee may also choose to conduct a random audit of your research;
- where a minor change to an approved protocol is proposed, you are required to submit a request for approval of this change in writing to the Secretary. Minor changes will be assessed on a case by case basis and interim approval may be granted subject to ratification at the next meeting of the Committee; and
- major changes to any approved protocol require a new application to be submitted and approved by the University Research Ethics Committee.

**Queensland University of Technology**

---

GARDENS POINT CAMPUS 2 GEORGE STREET GPO BOX 2434 BRISBANE Q 4001 AUSTRALIA PHONE (07) 3864 2111 FAX (07) 3864 1510

Campuses: Gardens Point (city), Kelvin Grove, Carseldine World Wide Web: <http://www.qut.edu.au/>  
QUT International: Locked Bag No 2 Red Hill Q 4059 Australia Phone +61 7 3864 3142 Fax +61 7 3864 3529

Please do not hesitate to contact me if you have any further queries in relation to this matter.

Yours sincerely

**Gary Allen**  
Secretary, University Research Ethics Committee  
QUT Secretariat  
Telephone: (07) 3864 2902  
Facsimile: (07) 3864 1818  
Email: [gx.allen@qut.edu.au](mailto:gx.allen@qut.edu.au)

cc Assoc Prof Peter Davies, School of Human Movement Studies, QUT Kelvin Grove

## **Appendix II**

### **Mater Adult Hospital ethics approval**

**MATER ADULT HOSPITAL RESEARCH ETHICS COMMITTEE**

16 July 1998

Miss Sandra Hayes  
19 Chinook Street  
Everton Hills QLD 4053

Dear Miss Hayes

At its 14 July 1998 meeting, the Mater Adult Hospital Research Ethics Committee considered your response to its queries in relation to the protocol "Exercise, functional capacity, quality of life, and cancer patients" (Ref No 115A).

The Committee was satisfied that your response addressed its concerns, subject to clarification in the patient information sheet that extra blood will be taken. The Director of Pathology requested that you liaise with the Department about the logistics of collecting the blood samples. Subject to the conditions above, the Committee resolved to approve this study.

This approval is valid for the duration of the project, or three years, whichever is earlier. Please forward the revisions/additional information outlined above to the Coordinator of the Mater Research Secretariat by **30 July 1998**.

Please note the following conditions of approval.

- Any departure from the protocol detailed in your proposal must be reported immediately to the Committee.
- When you propose a change to an approved protocol, which you consider to be minor, you are required to submit a written request for approval to the Chairperson, through the Secretary. Such requests will be considered on a case by case basis and interim approval may be granted subject ratification at the next meeting of the Committee.
- Where substantive changes to any approved protocol are proposed, you are required to submit a full, new proposal for consideration by the Research and Ethics Committee.
- You are required to advise the Hospital Ethicist immediately if any complaints made, or expressions of concern raised, in relation to the study, or if any adverse events occur.
- Under the *NHMRC Statement on Human Experimentation and Supplementary Notes*, research ethics committees are responsible for monitoring research to ensure continued compliance with ethical standards, and to determine the method of monitoring appropriate to each project. You are therefore required to provide written reports on the progress of the approved project at least annually. The Committee may also choose to conduct an interim audit of your research.



**Mater  
Misericordiae  
Hospitals**  
Raymond Terrace  
South Brisbane  
Queensland 4101  
Australia

Telephone  
07 - 3840 8111

Facsimile  
07 - 3840 1555

Mater Research Secretariat  
Room 204, Aubigny Place  
Mater Hospitals Complex  
Raymond Terrace  
SOUTH BRISBANE QLD 4101

Telephone: 3840 1585/1589  
Facsimile: 3840 1840  
Email: 1dmeap@mater.org.au  
or 2eplap@mater.org.au

Mater Adult Hospital  
Mater Children's Hospital  
Mater Mothers' Hospital  
Mater Mothers' Private Hospital  
Mater Private Hospital

Conducted by the Corporation  
of the Trustees of the Order  
of the Sisters of Mercy  
in Queensland

LAAP\_DMEWAHCCORRESPOICORRJULDOC

I would be grateful if you would confirm the commencement date of the project.  
(All correspondence should be directed to the Research Secretariat Coordinator,  
Room 204, Aubigny Place.)

Yours sincerely



**Mr Chris Coyne**  
Chairperson, Mater Adult Hospital Research Ethics Committee



**Mater**  
**Misericordiae**  
**Hospitals**  
Raymond Terrace  
South Brisbane  
Queensland 4101  
Australia

Telephone  
07 - 3840 8111

Facsimile  
07 - 3840 1595

*Mater Adult Hospital*  
*Mater Children's Hospital*  
*Mater Mothers' Hospital*  
*Mater Mothers' Private Hospital*  
*Mater Private Hospital*

L:\AP\_DMEWAH\CORRESPONDENCE\CORR\JUL.DOC

Conducted by the Corporation  
of the Trustees of the Order  
of the Sisters of Mercy  
in Queensland

## **Appendix III**

### **Wesley Private Hospital ethics approval**

27 August 1998

Project No. 98/09

Ms Sandi Hayes  
PhD Student  
Queensland University of Technology  
email: sc.hayes@student.qut.edu.au

Dear Sandi

**RESEARCH PROPOSAL:** *The role of exercise in enhancing functional capacity and quality of life, in the rehabilitation phase of patients who have undergone an autologous peripheral blood stem cell transplant.*

I am pleased to advise that the abovenamed research proposal has been reviewed and was granted approval by the Multi-Disciplinary Ethics Committee of The Wesley Hospital Board at its meeting on 13 August 1998.

It is a strict condition of approval that any departure from the protocol detailed in the proposal submitted for approval be reported immediately to the Committee. If there is any change to the status of the project, this should be reported.

Approval for the project is given subject to your agreement to The Wesley Hospital requirements for the monitoring of research, which have been based on the Australian Health Ethics Committee guidelines, a copy of which is enclosed. Please note the requirement to submit a report annually or at the completion of the project, as appropriate.

With best wishes.

Yours sincerely

**Douglas Killer MBBS FRACP**  
Medical Superintendent  
Chairman, Multidisciplinary Ethics Committee

encl.

**The Wesley Hospital Multidisciplinary Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's Statement on Human Experimentation and Supplementary Notes.**



*Celebrating  
20 years  
of care*

451 CORONATION DRIVE,  
AUCHENFLOWER QLD 4066  
PO Box 499  
TOOWONG QLD 4066  
TELEPHONE: (07) 3232 7926  
FAX: (07) 3232 7908  
INTERNET HOME PAGE  
<http://www.wesley.com.au>



A UNITING CHURCH HOSPITAL

## **Appendix IV**

### **Subject information letter and package**

Hello, my name is Sandi Hayes, and I am currently undertaking a research project entitled "Cancer, Functional Capacity, Quality of Life and Exercise". I have completed a Human Movement Studies university degree which specialises in prescribing exercise for particular populations. Throughout this degree I became extremely interested in the role of exercise for cancer patients. As my interest was developed and I began to study the area further, it was evident that research within this field is limited.

Over the last couple of years, I have been involved with a number of cancer rehabilitation programs available throughout Brisbane. During this time I spoke to patients about the importance of physical activity and the role that exercise can play in returning people back to their 'normal' functional capacity, that will allow them to return to work, or simply to perform daily activities without becoming fatigued. My work as the Exercise Physiologist with a particular cancer rehabilitation program, allowed me to see patients that had undergone extensive treatment, improve their fitness, strength and mobility, whilst becoming less fatigued throughout their day.

This study and work with cancer patients, has continued to stimulate my interest in the area. However, important documentation of these results is still not available. Therefore, I decided to enter into a PhD program, which is a 3 year degree, researching a particular topic. I am writing to invite you to join me in my research endeavour to document exactly how exercise can improve patient's functional capacity and quality of life. Enclosed is a copy of a subject information package that describes what involvement within this project entails. It is quite heavy reading and I would be happy to go through the package with you personally.

There are two hospitals (Wesley Private Hospital and Mater Adult Hospital) and the Queensland University of Technology involved with the implementation of this study. Dr Ian Bunce and Dr John Bashford (Wesley), and Dr Kerry Taylor (Mater) have assisted me in developing this project and can be spoken to if you have any concerns. I hope you will take the time to read the subject information package as I feel involvement within this research project will assist you in improving your functional capacity following your transplant. Again, I would love to personally speak with you about the project and can be contacted at any time.

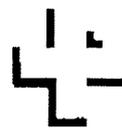
I look forward to speaking with you,  
Sandi Hayes (Hm: 3353 1687, Wk: 3864 5833, Mb: 0413 092 189)



1349H



Mater  
Misericordiae  
Hospitals



The  
WESLEY HOSPITAL

**SUBJECT INFORMATION PACKAGE**

**Project Title:**

"Cancer, Functional Capacity, Quality of Life and Exercise"

**Principal Investigator:-**  
**Qualifications:-**

Miss Sandra Christine Hayes  
Bachelor of Applied Science (Human Movement Studies)  
Contact No.: 3864 5833

**Project Supervisors:-**

Associate Professor Peter Davies  
Contact No.: 3864 5830

Professor Anthony Parker  
Contact No.: 3864 3282

**School/Centre for Research:**

Queensland University of Technology  
Faculty of Health  
School of Human Movement Studies  
Kelvin Grove Campus  
Victoria Park Road  
KELVIN GROVE QLD 4059  
ph: 3864 3360

**Project Objectives and Rationale:**

Advances in medical technology is represented by increasing survival rates from those diagnosed with cancer. Unfortunately, significant side effects are still experienced as a result of cancer and its associated treatment and physical inactivity. Physical side effects that may be experienced include a reduced ability to participate in daily activities such as household chores and/or performing a days work. In addition, reduced self esteem, self confidence, and mood, may constitute some psychological side effects.

**Faculty of Health**  
**Queensland University of Technology**

---

KELVIN GROVE CAMPUS VICTORIA PARK ROAD KELVIN GROVE Q 4059 AUSTRALIA PHONE (07) 3864 5779 FAX (07) 3864 5662

**Campuses:** Gardens Point (city), Kelvin Grove, Carseeldine **World Wide Web:** <http://www.qut.edu.au/>  
**QUT International:** Victoria Park Road Kelvin Grove Q 4059 Australia Phone +61 7 3864 3142 Fax +61 7 3864 3529



1349H

It is the primary purpose of this investigation, to demonstrate that participation in an appropriate and progressive exercise program has a significant role in improving functional capacity and ultimately quality of life, in patients who have undergone an autologous peripheral blood stem cell transplant.

**Experimental Procedures:**

Eligible subjects will be undergoing an autologous peripheral blood stem cell transplant, and will participate in a 5 month exercise intervention. Numerous types of exercise programs exist and it is therefore important to assess which form of exercise program is ideal in the rehabilitation phase of cancer. For this reason, subjects will be placed into one of two experimental groups:

- A. Group A will be involved in an aerobic exercise (walking, cycling, etc) and a resistance exercise (lifting light weights in a controlled fashion) program;
- B. and Group B will perform a stretching/mobility exercise program.

In order to carry out the program properly, if you decide to participate in the program, you will not be able to choose which group you would like to participate in. As the investigator is notified that you are wanting to participate in the project, you will be placed into one of the groups in a randomised manner.

Throughout the study, three testing sessions will be scheduled - pre-transplant, post-transplant and following the 5 month intervention period. During these sessions, your T cell (an immune cell) number and function; bone turnover; body composition; muscular strength; flexibility; heart, lung and circulatory function; energy expenditure and quality of life; will be assessed in the following manner:

***Bone turnover (formation rate), and T cell number and function:-***

Blood samples will be obtained at 7 different testing phases, which will be scheduled prior to the transplant, post transplant, and at the end of each month during the intervention period. These blood samples will be obtained during routine blood tests at the hospital and therefore you will not be required to undergo any extra blood tests. Blood obtained in the pre- and post-transplant period, and at the end of the 5 month intervention, will be used to assess bone formation rate. In addition, blood samples obtained at the 7 testing phases will be used to assess T cell number and function.

**Faculty of Health  
Queensland University of Technology**

---

KELVIN GROVE CAMPUS VICTORIA PARK ROAD KELVIN GROVE Q 4059 AUSTRALIA PHONE (07) 3864 5779 FAX (07) 3864 5662

Campuses: Gardens Point (city), Kelvin Grove, Carseldine World Wide Web: <http://www.qut.edu.au/>  
QUT International: Victoria Park Road Kelvin Grove Q 4059 Australia Phone +61 7 3864 3142 Fax +61 7 3864 3529



1349H

At the end of each day, for the duration of the study, you will be required to complete an illness questionnaire. It is a one page questionnaire, and will take little time to complete (expected duration of 30 seconds). The results of the questionnaire will be used to assess whether you are feeling ill or not on that particular day. In addition, we will be able to determine whether participation in exercise, has any influence over your feeling of wellness.

**Energy Expenditure and Bone turnover (resorption rate):**

In order to assess energy expenditure, two non-toxic isotopes of hydrogen and oxygen will be administered to you approximately 2 weeks prior to your transplant, as soon as possible following the transplant and 2 weeks prior to the completion of your 5 month intervention period. Prior to orally ingesting these isotopes, you will be asked to provide a urine sample which will be used to assess the resorption rate of bone. Once the isotopes have been ingested, you will then be required to provide one urine sample per day, for 14 days. These urine samples will be assessed to determine the difference between the elimination of the two isotopes, which reflects carbon dioxide production. By calculating carbon dioxide production, we are able to determine total energy expenditure.

**Body Composition:-**

Body composition assessment requires the calculation of fat tissue and fat free tissue, and will be performed in 2 ways. Firstly, one of the urine samples obtained as outlined above, in the pre-transplant, post-transplant, and following the 5 month intervention period, will be used to assess fat and fat-free mass. Secondly, skinfolds at six sites across the body, will be taken. The taking of skinfolds is a painless technique which requires the investigator to lift a fold of skin and underlying fat tissue and to measure the size of this fold.

**Muscular strength:-**

Muscular strength will be assessed by three methods and includes an isometric handgrip strength test, a 15 repetition maximum bench press, and 15 repetition maximum leg press. The handgrip test involves you to maximally grip a hand dynamometer which will assess gripping force (the test is similar to opening a tight jar lid). The bench press and leg press exercises, are two exercises which are commonly performed to improve upper and lower body strength, respectively. You will be instructed to perform the exercise

**Faculty of Health  
Queensland University of Technology**

---

KELVIN GROVE CAMPUS VICTORIA PARK ROAD KELVIN GROVE Q 4059 AUSTRALIA PHONE (07) 3864 5779 FAX (07) 3864 5662

Campuses: Gardens Point (city), Kelvin Grove, Carseldine World Wide Web: <http://www.qut.edu.au/>  
QUT International: Victoria Park Road Kelvin Grove Q 4059 Australia Phone +61 7 3864 3142 Fax +61 7 3864 3529



1349H

with the initial weight of the lift being dependent upon your estimated strength. The investigator will gradually add or reduce weight until a weight is achieved that you can lift exactly 15 times (not less than, or more than, 15 times). This part of the project is designed to evaluate the potential for participation in an exercise program to improve body composition (increase muscle mass particularly) and in turn to improve muscular strength (which will determine the ability to perform activities like opening a tight jar, carrying a bag full of groceries, lifting and moving objects).

**Flexibility:-**

Range of motion will be assessed by 6 different mobility tests. These tests are implemented to assess the mobility of the joints and muscles which are particularly important for effective and efficient participation in normal daily activities such as bending over to tie up shoe laces, reaching for the seat belt, putting on underwear, and walking. That is, lower back, shoulder, ankle and hip mobility will be assessed. Each test will require you to move a specific joint through its maximum range of motion and to hold it at that position until the point has been measured. It is a non-invasive and painless procedure.

**Heart, lung and circulatory function:-**

The assessment of this function will require you to participate in three graded exercise treadmill tests across the three usual testing periods. A graded treadmill exercise test, is an exercise test that begins at a light workload, but gradually increases in workload, until you are working maximally (as hard as you possibly can). Once it is noted that you are no longer able to perform more work, the test is ceased. Throughout the test, you will be required to breath through a mouth piece which is transporting expired air into a gas analyser. The test is able to assess maximal oxygen consumption and thus cardiovascular (heart and circulation) and cardiorespiratory (heart and lung) function. Additionally, electrocardiography - ECG (looking at the electrical activity of the heart), heart rate and blood pressure will be continually assessed, and a doctor will be present to analyse the ECG as the test progresses, to ensure the test is performed with maximal safety. This test will be able to measure the potential for exercise participation to improve cardiovascular and cardiorespiratory endurance (the ability to perform prolonged periods of work such as mowing the yard, vacuuming, performing a days work, etc).

**Faculty of Health  
Queensland University of Technology**

---

KELVIN GROVE CAMPUS VICTORIA PARK ROAD KELVIN GROVE Q 4059 AUSTRALIA PHONE (07) 3864 5779 FAX (07) 3864 5662

Campuses: Gardens Point (city), Kelvin Grove, Carseldine World Wide Web: <http://www.qut.edu.au/>  
QUT International: Victoria Park Road Kelvin Grove Q 4059 Australia Phone +61 7 3864 3142 Fax +61 7 3864 3529



**Quality of Life:-**

The 'CARES' is a quality of life questionnaire which has been specifically designed for assessing quality of life in cancer patients. Unfortunately, to obtain as much information as possible, it is a lengthy questionnaire and will take you approximately 30 minutes to complete. The questionnaire is a subjective analysis by you, and will be used to measure the impact of physical activity on your quality of life in all wellness areas including physical, social, spiritual, occupational, etc.

**Patient Commitment of Time and Expense:**

The primary commitment will be that of time. Unfortunately, present guidelines suggest that exercise intervention programs need to be scheduled for 5 months, in order to observe significant changes in physiological data. For this reason, you will be required to exercise 3 times per week for a period of 5 months. Within this first month, it will be necessary for you to attend supervised exercise sessions at the QUT, Human Movement Clinic. Each session will last approximately 1 hour. Following this familiarisation period, if you would prefer to exercise in community centers, or where appropriate, within the home environment, arrangements will be made when possible. In addition to participation within these exercise sessions, you will be required to participate in the three testing dates, held within the laboratories at the QUT, School of Human Movement Studies. Approximately, 1.5-2 hours will be required to complete all scheduled tests. Exercise and testing sessions will be scheduled at times which are convenient to you.

Additionally, it is felt that the exercise sessions will be an enjoyable time when you are working towards attaining personal goals, and a time when you are able to socialise with other patients who have undergone similar experiences.

**Potential Complications of Procedures:**

Participation in physical activity programs, brings with it the risk of musculoskeletal injury. This risk will be minimised by ensuring that the exercise program developed is initiated at a level which is well tolerated, and will be progressed slowly to ensure that you are able to adapt to the increasing stimulus without risk of injury. As noted above, you will be asked to participate in three graded maximal treadmill exercise tests. At the end stages of this test, you will be working the heart, lungs, circulation and muscles maximally. Due to the high intensity of workload effort, it is likely that delayed muscle

**Faculty of Health  
Queensland University of Technology**

---

KELVIN GROVE CAMPUS VICTORIA PARK ROAD KELVIN GROVE Q 4059 AUSTRALIA PHONE (07) 3864 5779 FAX (07) 3864 5662

Campuses: Gardens Point (city), Kelvin Grove, Carseldine World Wide Web: <http://www.qut.edu.au/>  
QUT International: Victoria Park Road Kelvin Grove Q 4059 Australia Phone +61 7 3864 3142 Fax +61 7 3864 3529



1349H

soreness may occur following the test. This muscle soreness will be relieved with time, however, an appropriate warm-up and cool down will be undertaken before and after the test, respectively, to minimise this soreness. All exercise programs and testing procedures have been designed to ensure that the chance of developing a musculoskeletal injury is minimal.

In the case of an injury occurring, the investigator is trained in first-aid and will therefore be able to initiate the appropriate primary treatment immediately. Following primary treatment, arrangements will be made for you to see the appropriate health professional.

**Potential Benefits Derived from Participation:**

- The benefits of exercise may enhance your ability to cope with the rigors of cancer treatment, and will maximise your independence post-treatment.
- Involvement in an exercise program has the potential to minimise the loss of muscle mass and thus strength, it may stimulate appetite, and optimise your ability to perform daily activities.
- This research will assist in providing knowledge of the impact that undergoing an APBST has on the immune system, skeletal system, cardiovascular system and quality of life. It will also determine the potential of an exercise program in improving these systems back to pre-transplant levels.
- This investigation will allow the energy cost of undergoing an APBST to be measured and therefore will assist medical professionals in determining the amount of energy intake needed to maintain you in a state of energy balance - meaning what amount of food intake is required for you to maintain a steady body weight. It will also allow the measurement cost of participating in an exercise program to ensure that the exercise being prescribed is beneficial to your health.
- Long term benefits include the prevention of further debilitating conditions including cardiovascular diseases, diabetes, and osteoporosis, to name a few.

**Confidentiality of Records and Patient Information:**

Data obtained from all investigations will remain confidential so that the primary investigator will be the only individual who has access to the raw data. Additionally, data will be kept within a locked filing cabinet and locked room during times when it is being stored. Specialists or GPs will be able to gain access to the data only when

**Faculty of Health  
Queensland University of Technology**

---

KELVIN GROVE CAMPUS VICTORIA PARK ROAD KELVIN GROVE Q 4059 AUSTRALIA PHONE (07) 3864 5779 FAX (07) 3864 5662

Campuses: Gardens Point (city), Kelvin Grove, Carseldine World Wide Web: <http://www.qut.edu.au/>  
QUT International: Victoria Park Road Kelvin Grove Q 4059 Australia Phone +61 7 3864 3142 Fax +61 7 3864 3529



1349H

permission has been granted by the relevant patient. When assessing, analysing and discussing results, each patient will be allocated a number, and that patient number will be used to discuss specific results if the need arises. Otherwise, results will be discussed according to the intervention groups, A and B.

**Voluntary Participation:**

You have been given this subject information package, as you have met the appropriate inclusion criteria for the investigation. However, participation in this project is entirely voluntary. If you decide to participate, you are free to withdraw consent before or during the experiment, at any time. Your participation or withdrawal of consent will not influence your present and/or future involvement with Queensland University of Technology, Mater Hospital or the Wesley Hospital.

**Enquires:**

Questions concerning the procedures and/or rationale used in this investigation are welcome at any time. Please ask for clarification of any point you feel is not explained to your satisfaction. Your initial contact person is the investigator, Sandi Hayes, ph: 3864 5833. Subsequent enquires may be directed to the Principal Supervisor, Peter Davies, ph: 3864 5830.

**Faculty of Health  
Queensland University of Technology**

---

KELVIN GROVE CAMPUS VICTORIA PARK ROAD KELVIN GROVE Q 4059 AUSTRALIA PHONE (07) 3864 5779 FAX (07) 3864 5662

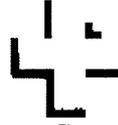
Campuses: Gardens Point (city), Kelvin Grove, Carseldine World Wide Web: <http://www.qut.edu.au/>  
QUT International: Victoria Park Road Kelvin Grove Q 4059 Australia Phone +61 7 3864 3142 Fax +61 7 3864 3529



1349H



MATER  
Misericordiae  
Hospitals



The  
WESLEY HOSPITAL

## INFORMED CONSENT

The researcher conducting this investigation supports the principles governing the ethical conduct of research outlined by the National Health and Medical Research Council (NHMRC). Additionally, the protection of the subject's interests, comfort and safety will be upheld at all times.

This form and the accompanying Subject Information Package are given to you for your own protection. A detailed outline of the experimental procedures, potential benefits and possible risks are clearly outlined within the Subject Information Package. Your signature below indicates the following:

1. you have read the Subject Information Package;
2. you have been given the opportunity to discuss its contents with either the researcher or her supervisor prior to commencing the experiment;
3. you clearly understand these procedures and potential risks;
4. you voluntarily agree to participate in this project; and
5. you understand that your participation may be terminated at any point in time throughout the project, without jeopardising your involvement with the Queensland University of Technology, the Mater Hospital or the Wesley Hospital.

Any enquires or further questions may be initially directed to the researcher, Sandi Hayes, on 3864 5833, or 3353 1687, or to the principal supervisor, Associate Professor Peter Davies, on 3864 5830. Any complaints regarding the conduct of the research may be directed to the Head of the School of Human Movement Studies, Professor Tony Parker or the Secretary of the University Research Ethics Committee, on 3864 2902. Additionally, Dr Kerry Taylor can be contacted if you are a Mater Patient, or Dr Ian Bunce, if you are a Wesley Patient.

### Faculty of Health Queensland University of Technology

KELVIN GROVE CAMPUS VICTORIA PARK ROAD KELVIN GROVE Q 4059 AUSTRALIA PHONE (07) 3864 5779 FAX (07) 3864 5662

Campuses: Gardens Point (city), Kelvin Grove, Carseldine World Wide Web: <http://www.qut.edu.au/>  
QUT International: Victoria Park Road Kelvin Grove Q 4059 Australia Phone +61 7 3864 3142 Fax +61 7 3864 3529



1349H



Mater  
Misericordiae  
Hospitals



I agree to participate in the experimental procedures outlined in the Subject Information Package.

<b>Patient:</b>	
Last Name: _____	Given Names: _____
Date of Birth: ____ / ____ / ____	
Address: _____	
Signature: _____	Date: ____ / ____ / ____
<b>Name and number of contact person in case of an emergency:</b>	
Name: _____	Phone Number: _____
General Practitioner: _____	Phone Number: _____
<b>Witness:</b>	
Last Name: _____	Given Names: _____
Signature: _____	Date: ____ / ____ / ____

**Faculty of Health  
Queensland University of Technology**

KELVIN GROVE CAMPUS VICTORIA PARK ROAD KELVIN GROVE Q 4059 AUSTRALIA PHONE (07) 3864 5779 FAX (07) 3864 5662

Campuses: Gardens Point (city), Kelvin Grove, Carseldine World Wide Web: <http://www.qut.edu.au/>  
QUT International: Victoria Park Road Kelvin Grove Q 4059 Australia Phone +61 7 3864 3142 Fax +61 7 3864 3529

# **APPENDIX V**

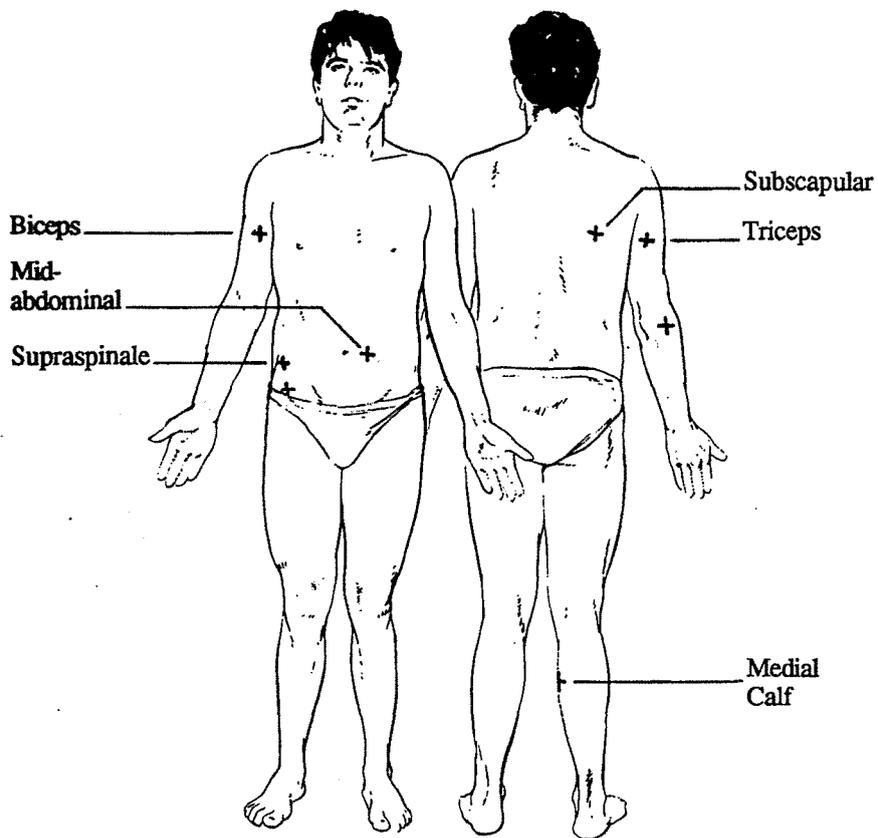
## **Assessment of body composition via the use of the skinfold technique**

The following six skinfolds were assessed using standard procedures, with calibrated Harpenden Skinfold Calipers for the calculation of the sum of skinfolds (SOS) and percentage body fat (%BF):

- ◆ *Triceps*: The vertical skinfold was raised with the left thumb and index finger such that the lateral surfaces of the thumb and finger are aligned with the intersection of the extended mid-acromiale-radiale line and the vertical line on the most posterior aspect of the arm, with the arm in the anatomical position. The caliper was applied such that the nearest edge of the caliper jaw is 1 cm from the marked site.
- ◆ *Biceps*: The vertical skinfold was raised on the anterior surface of the arm at the intersection of the extended mid-acromiale-radiale line and the vertical line in the middle of the belly of the biceps muscle. The lateral surfaces of the thumb and finger are aligned with the point of intersection. The caliper was applied 1 cm from the point of intersection.
- ◆ *Subscapular*: The inferior surface of the inferior angle of the scapula was palpated with the tip of the left thumb. A skinfold was raised below and lateral to the inferior angle of the scapula. The fold sloped downwards towards the side of the body. The caliper was applied 1 cm from the thumb and index finger.
- ◆ *Abdominal*: The vertical skinfold was raised at a marked site on a horizontal line 5 cm to the right of the centre of the umbilicus. The lateral surfaces of the left thumb and index finger were aligned with the marked site. The caliper was applied 1 cm below the marked site.
- ◆ *Supraspinale*: The iliospinale landmark was located first - the undersurface of the tip of the anterior superior iliac spine. It was located by palpating in a forward direction along the iliac crest. Then the supraspinale skinfold site was located. The anthropometric tape was positioned on a line from the anterior axillary fold to the iliospinale site. The point where the tape intersects with the imaginary horizontal line projected medially from the iliac crest was marked. The skinfold sloped downward in a medial direction and the caliper was applied 1 cm from the lateral surfaces of the left thumb and index finger.
- ◆ *Medial Calf*: This site was on the medial surface of the calf at the level of the greatest calf circumference. The subject was asked to stand on a box with feet slightly apart and body mass evenly distributed. The anthropometric tape was used to determine the level of maximum right calf circumference. With the tape around the calf, a horizontal mark was made just below the tape on the most medial surface of the calf. The subject was then asked to stand on the floor and place the right foot on a chair with the knee bent at 90°, calf relaxed. A skinfold was raised with the lateral surfaces of the left thumb and index finger aligned with the horizontal mark. The caliper was applied 1 cm below the horizontal mark.

Figure 4.1 provides an illustration of the anatomical location of each site.

Figure 4.1 Skinfold Sites



Taken from Gore & Edwards (1992)<sup>144</sup>

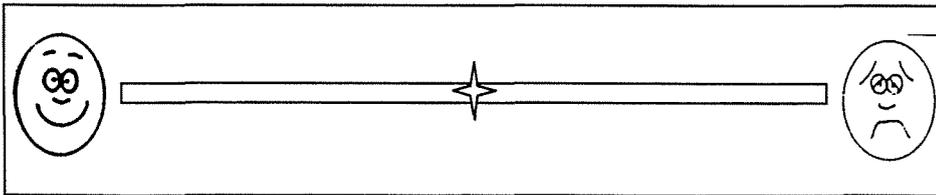
## **APPENDIX VI**

### **Assessment of perceived exertion via the use of the visual analogue scale**

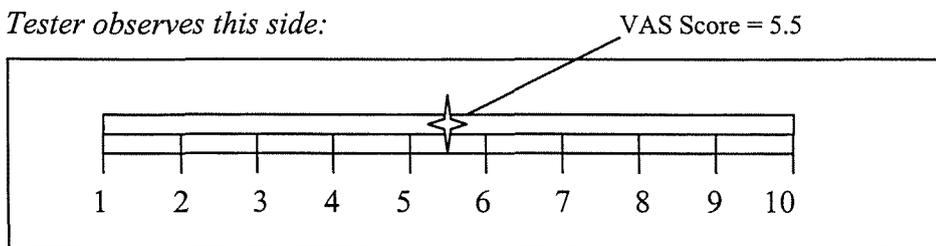
The VAS is a technique used to assess the patient's perception of effort and is a continuum that ranges from 0 - no exertion (smiley face), to 10 - maximum exertion (hot/tired face) (shown in Figure 5.2). While it is similar to using the revised Borg's rating of perceived exertion scale (RPE) (shown in Figure 5.1), several differences exist. A graphical presentation of the revised RPE scale and the VAS is provided below. Use of the VAS requires the patient to observe a straight line with no divisions across the scale. When asked, the patient must move a marker along the line to the point that most closely represents their perceived level of exertion. On the tester's side of the VAS, the scaling is clearly marked in millimeters and therefore the positioning of the marker by the patient can be quantified without the patient knowing the exact score given. The implementation of this procedure assisted in minimising bias towards how the patient was feeling from one stage to the next. Once the patient reported their perceived exertion, the marker was returned to the beginning of the scale, '0', thereby limiting the ability of one score to influence the next.

**Figure 5.1** Visual analogue scale

*Patient observes this side:*



*Tester observes this side:*



**Figure 5.2** Borg's 10 point RPE scale

RPE – 10 Point Scale	
0	Nothing at all
0.5	Very, Very light
1	Very light
2	Light
3	Moderate
4	Somewhat Heavy
5	Heavy
6	
7	Very Heavy
8	
9	
10	Very, Very Heavy
--	Maximal

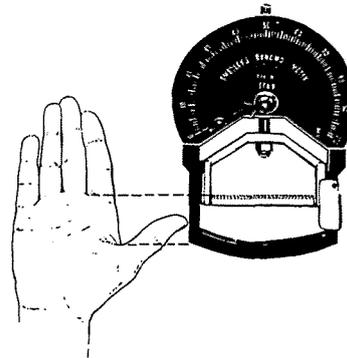
\* The adapted version taken from Wilmore & Costill (1994)<sup>422</sup>

# **APPENDIX VII**

## **Assessment of handgrip strength**

**Handgrip strength test (Smedley's Dynamo Meter TTM)<sup>142</sup>:**

- A verbal description and practical demonstration of the test was given;
- the handgrip apparatus was adjusted to suit the patient's handgrip and the dial was set at zero;
- the patient was then instructed to maximally grip the apparatus;
- in order to standardise the procedure no encouragement was given;
- and, the test was repeated three times for both the right and left hand.



All patients were right hand dominant, and thus the best score achieved for the right hand was adjusted for FFM variances. The averaged score of the best right and left hand grip strength results were also recorded and used for comparison with normative data. These values were then used during statistical analysis.

# **APPENDIX VIII**

## **CARES QoL questionnaire**

**CARES**  
**Cancer Rehabilitation Evaluation System**  
**For Research**

Developed  
by  
C. Anne Coscarelli Schag, Ph.D.  
and  
Richard L. Heinrich, M.D.

Copyright © CARES Consultants, 1988

2210 Wilshire Blvd, Suite 359, Santa Monica, California 90403 (310) 450-7410

# CARES

## Cancer Rehabilitation Evaluation System For Research

Patient ID#: \_\_\_\_\_

Date: \_\_\_\_\_

### Instructions

Below is a list of Problem Statements that describe situations and experiences of individuals who have or have had cancer. Read each statement and circle the number that best describes **HOW MUCH EACH STATEMENT APPLIES TO YOU** during the **PA MONTH, INCLUDING TODAY**. Some sections will not apply to you. Please skip these sections and proceed to the next one as directed.

### Example

How much does it apply to you?	Not at all	A little	A fair amount	Much	Very much
1. I have difficulty walking .....	0	①	2	3	4
2. I find that food tastes bad .....	0	1	2	3	④

**How much does it apply to you?**

Not at all  
A little  
A fair amount  
Much  
Very much

- 1. I have difficulty bending or lifting .....0 1 2 3 4
- 2. I have difficulty walking and/or moving around .....0 1 2 3 4
- 3. I have difficulty doing physical activities such as running and playing sports .....0 1 2 3 4
- 4. I do not have the energy I used to .....0 1 2 3 4
- 5. I have difficulty driving .....0 1 2 3 4
- 6. I have difficulty doing household chores .....0 1 2 3 4
- 7. I have difficulty bathing, brushing my teeth, or grooming myself .....0 1 2 3 4
- 8. I have difficulty preparing meals .....0 1 2 3 4
- 9. I am not interested in recreational activities like I used to be .....0 1 2 3 4
- 10. I do not engage in the recreational activities that I used to .....0 1 2 3 4
- 11. I do not have enough enjoyable activities to fill the day .....0 1 2 3 4
- 12. I have difficulty planning activities because of the cancer or its treatments .....0 1 2 3 4
- 13. I cannot gain weight .....0 1 2 3 4
- 14. I am continuing to lose weight .....0 1 2 3 4
- 15. I find food unappealing .....0 1 2 3 4
- 16. I find that food tastes bad .....0 1 2 3 4
- 17. I find it difficult to swallow .....0 1 2 3 4
- 18. I find that the cancer or its treatments keep me from working .....0 1 2 3 4
- 19. I find that cancer or its treatments interfere with my ability to work .....0 1 2 3 4
- 20. I frequently have pain .....0 1 2 3 4
- 21. I have chronic pain from scars and surgery .....0 1 2 3 4
- 22. I have pain that is not controlled by pain medication .....0 1 2 3 4

**How much does it apply to you?**

Not at all  
A little  
A fair amount  
Much  
Very much

- |  |   |   |   |   |   |
|--|---|---|---|---|---|
| 23. I have pain that is controlled by pain medication .....  | 0 | 1 | 2 | 3 | 4 |
| 24. I find that my clothes do not look good on me.....   | 0 | 1 | 2 | 3 | 4 |
| 25. I find that my clothes do not fit .....  | 0 | 1 | 2 | 3 | 4 |
| 26. I have difficulty finding clothes to fit.....  | 0 | 1 | 2 | 3 | 4 |
| 27. I find that the medical team withholds information from me about<br>the cancer .....                 | 0 | 1 | 2 | 3 | 4 |
| 28. I find that doctors don't explain what they are doing to me .....                                    | 0 | 1 | 2 | 3 | 4 |
| 29. I find that nurses don't explain what they are doing to me .....                                     | 0 | 1 | 2 | 3 | 4 |
| 30. I have difficulty asking doctors questions .....   | 0 | 1 | 2 | 3 | 4 |
| 31. I have difficulty asking nurses questions .....  | 0 | 1 | 2 | 3 | 4 |
| 32. I have difficulty expressing my feelings to the doctors and nurses .....                             | 0 | 1 | 2 | 3 | 4 |
| 33. I have difficulty telling my doctor about new symptoms .....   | 0 | 1 | 2 | 3 | 4 |
| 34. I have difficulty understanding what the doctors tell me about the<br>cancer or its treatments ..... | 0 | 1 | 2 | 3 | 4 |
| 35. I have difficulty understanding what the nurses tell me about the<br>cancer or its treatments.....   | 0 | 1 | 2 | 3 | 4 |
| 36. I would like to have more control over what the doctors do to me .....                               | 0 | 1 | 2 | 3 | 4 |
| 37. I would like to have more control over what the nurses do to me .....                                | 0 | 1 | 2 | 3 | 4 |
| 38. I am embarrassed to show my body to others because of my illness .....                               | 0 | 1 | 2 | 3 | 4 |
| 39. I am uncomfortable showing my scars to others .....  | 0 | 1 | 2 | 3 | 4 |
| 40. I am uncomfortable with the changes in my body .....   | 0 | 1 | 2 | 3 | 4 |
| 41. I frequently feel anxious .....  | 0 | 1 | 2 | 3 | 4 |
| 42. I frequently feel depressed .....  | 0 | 1 | 2 | 3 | 4 |
| 43. I frequently feel angry .....  | 0 | 1 | 2 | 3 | 4 |

## How much does it apply to you?

Not at all  
A little  
A fair amount  
Much  
Very much

- |  |   |   |   |   |   |
|--|---|---|---|---|---|
| 44. I frequently feel upset .....  | 0 | 1 | 2 | 3 | 4 |
| 45. I frequently feel overwhelmed by my emotions and feelings about the cancer .....         | 0 | 1 | 2 | 3 | 4 |
| 46. I have difficulty sleeping .....   | 0 | 1 | 2 | 3 | 4 |
| 47. I have difficulty concentrating .....  | 0 | 1 | 2 | 3 | 4 |
| 48. I have difficulty remembering things .....   | 0 | 1 | 2 | 3 | 4 |
| 49. I have difficulty thinking clearly .....   | 0 | 1 | 2 | 3 | 4 |
| 50. I have difficulty telling my friends or relatives to come over less often .....          | 0 | 1 | 2 | 3 | 4 |
| 51. I have difficulty telling my friends or relatives to leave when I do not feel well ..... | 0 | 1 | 2 | 3 | 4 |
| 52. I have difficulty asking my friends or relatives to do something fun with me .....       | 0 | 1 | 2 | 3 | 4 |
| 53. I do not know what to say to my friends or relatives .....                               | 0 | 1 | 2 | 3 | 4 |
| 54. I have difficulty asking friends or relatives to do things for me .....                  | 0 | 1 | 2 | 3 | 4 |
| 55. I have difficulty telling my friends or relatives about the cancer .....                 | 0 | 1 | 2 | 3 | 4 |
| 56. I have difficulty asking my friends or relatives to come over more often .....           | 0 | 1 | 2 | 3 | 4 |
| 57. I find that my friends or relatives tell me I'm looking well when I'm not.....           | 0 | 1 | 2 | 3 | 4 |
| 58. I find that my friends or relatives withhold information from me .....                   | 0 | 1 | 2 | 3 | 4 |
| 59. I find that my friends or relatives avoid talking with me about the cancer .....         | 0 | 1 | 2 | 3 | 4 |
| 60. I find that my friends or relatives do not visit often enough .....                      | 0 | 1 | 2 | 3 | 4 |
| 61. I find that my friends or relatives do not call often enough.....                        | 0 | 1 | 2 | 3 | 4 |

**How much does it apply to you?**

*Not at all  
A little  
A fair amount  
Much  
Very much*

- 62. I find that my friends or relatives are uncomfortable when they visit me .....0 1 2 3 4
- 63. I find that friends or relatives have difficulty talking with me about my illness .....0 1 2 3 4
- 64. I feel uncomfortable when I see other patients getting treatments .....0 1 2 3 4
- 65. I become nervous when I have to go to the hospital .....0 1 2 3 4
- 66. I become nervous when I am waiting to see the doctor .....0 1 2 3 4
- 67. I become nervous when I am waiting to find out the results of tests .....0 1 2 3 4
- 68. I become nervous when I am having diagnostic tests .....0 1 2 3 4
- 69. I become nervous when I get my blood drawn .....0 1 2 3 4
- 70. I worry about whether my treatments are working .....0 1 2 3 4
- 71. I worry about whether the cancer is progressing .....0 1 2 3 4
- 72. I worry about not being able to care for myself .....0 1 2 3 4
- 73. I worry about how my family will manage if I die .....0 1 2 3 4
- 74. I do not feel sexually attractive .....0 1 2 3 4
- 75. I do not think my partner(s) finds me sexually attractive .....0 1 2 3 4
- 76. I am not interested in having sex .....0 1 2 3 4
- 77. I do not think that my partner(s) is interested in having sex with me .....0 1 2 3 4
- 78. I sometimes don't show up for my doctor's appointment .....0 1 2 3 4
- 79. I sometimes don't show up for my treatments .....0 1 2 3 4
- 80. I sometimes don't take my medication as prescribed .....0 1 2 3 4
- 81. I sometimes don't follow my doctor's instructions .....0 1 2 3 4
- 82. I have financial problems .....0 1 2 3 4

**How much does it apply to you?**

Not at all  
A little  
A fair amount  
Much  
Very much

- 83. I have insurance problems .....0 1 2 3 4
- 84. I have difficulty with transportation to and from my medical appointments and/or other places .....0 1 2 3 4
- 85. I am gaining too much weight .....0 1 2 3 4
- 86. I find some diagnostic procedures extremely painful .....0 1 2 3 4
- 87. I have frequent episodes of diarrhea .....0 1 2 3 4
- 88. I have times when I do not have control of my bladder .....0 1 2 3 4

**Do you have children? Yes No**

*If No, skip to next section.*

- 89. I have difficulty taking care of the children and/or the grandchildren .....0 1 2 3 4
- 90. I have difficulty helping my children cope with my illness .....0 1 2 3 4
- 91. I have difficulty helping my children talk about my illness .....0 1 2 3 4

**Are you working or have you been employed during the last month? Yes No**

*If No, skip to next section.*

- 92. I have difficulty talking to my boss about the cancer .....0 1 2 3 4
- 93. I have difficulty talking to the people who work with me about the cancer .....0 1 2 3 4
- 94. I have difficulty telling my employer that I cannot do something because of my illness .....0 1 2 3 4
- 95. I have difficulty asking for time off from work for medical treatments ....0 1 2 3 4
- 96. I am worried about being fired .....0 1 2 3 4

CARES

How much does it apply to you?		Not at all A little A fair amount Much Very much				
Did you look for work during the past month?		Yes	No			
<i>If No, skip to next section.</i>						
97.	I have difficulty finding a new job since I have had cancer .....	0	1	2	3	4
98.	I find that employers are reluctant to hire people with a cancer history .....	0	1	2	3	4
Have you been sexually active since your cancer diagnosis?		Yes	No			
<i>If No, skip to next section.</i>						
99.	I find that the frequency of sexual activity has decreased .....	0	1	2	3	4
100.	I have difficulty becoming sexually aroused .....	0	1	2	3	4
101a.	I have difficulty getting or maintaining an erection ( <b>Males</b> ) .....	0	1	2	3	4
	<b>b.</b> I have difficulty getting lubricated ( <b>Females</b> )					
102.	I have difficulty reaching orgasm .....	0	1	2	3	4
Are you married or in a significant relationship?		Yes	No			
<i>If No, skip to next section.</i>						
103.	My partner and I have difficulty talking about our feelings .....	0	1	2	3	4
104.	My partner and I have difficulty talking about our fears .....	0	1	2	3	4
105.	My partner and I have difficulty talking about what will happen after my death .....	0	1	2	3	4
106.	My partner and I have difficulty talking about our future .....	0	1	2	3	4
107.	My partner and I have difficulty talking about the cancer and what might happen .....	0	1	2	3	4

### How much does it apply to you?

Not at all  
A little  
A fair amount  
Much  
Very much

108. My partner and I have difficulty talking about wills and financial arrangements .....0 1 2 3 4
109. I do not feel like embracing, kissing, or caressing my partner .....0 1 2 3 4
110. My partner does not feel like embracing, kissing or caressing me .....0 1 2 3 4
111. I am not interested in touching my partner .....0 1 2 3 4
112. My partner is not interested in touching me .....0 1 2 3 4
113. My partner and I are not getting along as well as we usually do .....0 1 2 3 4
114. My partner and I are upset with each other more often than usual .....0 1 2 3 4
115. My partner and I have so much time together that we get on each other's nerves .....0 1 2 3 4
116. My partner and I are more distant than usual .....0 1 2 3 4
117. My partner won't let me do activities that I am capable of doing .....0 1 2 3 4
118. My partner spends too much time taking care of me .....0 1 2 3 4
119. My partner does not take care of me enough .....0 1 2 3 4
120. I have difficulty asking my partner to take care of me .....0 1 2 3 4

**Are you single and not in a significant relationship?                      Yes    No**

***If No, skip to next section.***

121. I have difficulty initiating contact with potential dates .....0 1 2 3 4
122. I have difficulty meeting potential dates .....0 1 2 3 4
123. I am afraid to go to places that I used to visit to meet dates .....0 1 2 3 4
124. I have difficulty telling a date about the cancer or its treatments .....0 1 2 3 4
125. I am afraid to initiate a sexual relationship with someone .....0 1 2 3 4

How much does it apply to you?

Not at all  
A little  
A fair amount  
Much  
Very much

Have you had chemotherapy treatments in the last month?

Yes No

*If No, skip to next section.*

- 126. I become nervous when I get chemotherapy .....0 1 2 3 4
- 127. I become nauseated during and/or before chemotherapy .....0 1 2 3 4
- 128. I vomit during and/or before chemotherapy .....0 1 2 3 4
- 129. I feel sick when I think about my chemotherapy .....0 1 2 3 4
- 130. I feel nauseated after I receive chemotherapy.....0 1 2 3 4
- 131. I vomit after chemotherapy .....0 1 2 3 4
- 132. I feel tired after my chemotherapy.....0 1 2 3 4
- 133. I have other side effects after chemotherapy.....0 1 2 3 4
- 134. I have lost my hair and/or it is growing back slowly because of chemotherapy .....0 1 2 3 4

Have you had radiation therapy treatments in the last month?

Yes No

*If No, skip to next section.*

- 135. I feel fatigued after my radiation treatments.....0 1 2 3 4
- 136. I get nervous when I get radiation treatments .....0 1 2 3 4
- 137. I feel nauseous or vomit after my radiation treatments.....0 1 2 3 4

Do you have an ostomy?

Yes No

*If No, skip to next section.*

- 138. I have problems with ostomy care and maintenance .....0 1 2 3 4

How much does it apply to you?

Not at all  
A little  
A fair amount  
Much  
Very much

Do you have a prosthesis?

Yes No

*If No, skip to next section.*

139. I have difficulty with my prosthetic device (artificial limb, breast prosthesis, etc.) .....0 1 2 3 4

## **APPENDIX IX**

### **A summary of items in the CARES questionnaire**

## Items in Subscales and Higher-order Factors

<i>Subscales</i>	<i>N items</i>	<i>Items numbers on CARES</i>
<i>Physical</i>	26	1-26
Ambulation	4	1-4
Activities of daily living	4	5-8
Recreational activities	4	9-12
Weight loss	5	13-17
Difficulty working	2	18-19
Pain	4	20-25
Clothing	3	24-26
<i>Medical Interaction</i>	11	27-27
Problems obtaining information from medical team	3	27-29
Difficulty communicating with medical team	6	30-35
Control of medical team	2	36-37
<i>*Psychosocial</i>	44	38-73, 89-96
Body Image	3	38-40
Psychological distress	6	41-46
Cognitive problems	3	47-49
Difficulty communicating with friends/relatives	7	50-56
Difficulty interacting with friends/relatives	7	57-63
Anxiety in medical situations	6	64-69
Worry	4	70-73
*Interaction with children	3	89-91
*At work concerns	5	92-96
<i>*Sexual</i>	8	74-77, 99-102
Sex interest	4	74-77
Sexual dysfunction	4	99-102
<i>*Marital</i>	18	103-120
*Communication with partner	6	103-108
*Affection with partner	4	109-112
*Interaction with partner	4	113-116
*Overprotection by partner	2	117-118
*Neglect of care by partner	2	119-120
<i>Miscellaneous Subscales</i>		
*Dating	5	121-125
*Chemotherapy-related problems	9	126-134
*Radiation-related problems	3	135-137
Compliance	4	78-81
Economic barriers	4	82-83, 97-98
<i>Miscellaneous Items</i>	7	
Transportation		84
Gain weight		85
Procedures painful		86
Diarrhea		87
Bladder control		88
*Ostomy		138
*Prosthesis		139

# **APPENDIX X**

## **CARES score and profile sheet**

**PHYSICAL**

**Ambulation**

- \_\_\_ 1. diff bend or lift
- \_\_\_ 2. diff walk/move around
- \_\_\_ 3. diff do physical activ.
- \_\_\_ 4. reduction in energy

**Activities of Daily Living**

- \_\_\_ 5. diff driving
- \_\_\_ 6. diff household chores
- \_\_\_ 7. diff bathe, brush groom
- \_\_\_ 8. diff prepare meals

**Recreational Activities**

- \_\_\_ 9. no interest recreat activ
- \_\_\_ 10. not engage recreat activ
- \_\_\_ 11. not enough enjoyable activ
- \_\_\_ 12. diff planning activ

**Weight Loss**

- \_\_\_ 13. cannot gain weight
- \_\_\_ 14. continue to lose weight
- \_\_\_ 15. food unappealing
- \_\_\_ 16. food tastes bad
- \_\_\_ 17. diff swallowing

**Difficulty Working**

- \_\_\_ 18. cancer prevents work
- \_\_\_ 19. cancer interferes work

**Pain**

- \_\_\_ 20. frequently has pain
- \_\_\_ 21. chronic pain scars/surgery
- \_\_\_ 22. pain not controlled medication
- \_\_\_ 23. pain controlled medication

**Clothing**

- \_\_\_ 24. clothes not look good
- \_\_\_ 25. clothes not fit
- \_\_\_ 26. diff find clothes
- \_\_\_ SUM \_\_\_ # (1-4) 26 # Potential

**MEDICAL INTERACTION**

**Problems Obtaining Info from Medical Team**

- \_\_\_ 27. medical team withholds info
- \_\_\_ 28. doctors don't explain what do
- \_\_\_ 29. nurses don't explain what do

**Difficulty Communicating with Medical Team**

- \_\_\_ 30. diff ask doctors questions
- \_\_\_ 31. diff ask nurses questions
- \_\_\_ 32. diff express feelings MD/RN
- \_\_\_ 33. diff tell doctor new symptoms
- \_\_\_ 34. diff understand MD about cancer
- \_\_\_ 35. diff understand RN about cancer

**Control of Medical Team**

- \_\_\_ 36. wants more control over MD
- \_\_\_ 37. wants more control over RN
- \_\_\_ SUM \_\_\_ # (1-4) 11 # Potential

**\*MARITAL**

**Communication with Partner**

- \_\_\_ 103. diff talk feelings
- \_\_\_ 104. diff talk fears
- \_\_\_ 105. diff talk happen after death
- \_\_\_ 106. diff talk future
- \_\_\_ 107. diff talk cancer
- \_\_\_ 108. diff talk wills/financial matters

**Affection with Partner**

- \_\_\_ 109. doesn't feel like embrace,etc
- \_\_\_ 110. partner no feel like embrace, etc.
- \_\_\_ 111. no interest in touch partner
- \_\_\_ 112. partner no interest in touch

**Interaction with Partner**

- \_\_\_ 113. not get along as well usual
- \_\_\_ 114. upset with other more often
- \_\_\_ 115. so much time together, on nerves
- \_\_\_ 116. more distant than usual

**Overprotection by Partner**

- \_\_\_ 117. partner not let do activ capable of
- \_\_\_ 118. partner provides too much care

**Neglect of Care by Partner**

- \_\_\_ 119. partner takes too little care
- \_\_\_ 120. diff ask partner to take care
- \_\_\_ SUM \_\_\_ # (1-4) 18,0
- \_\_\_ # Potential Circle

**PSYCHOSOCIAL**

**Body Image**

- \_\_\_ 38. embarrassed to show body
- \_\_\_ 39. uncomfor show scars
- \_\_\_ 40. uncomfor with body changes

**Psychological Distress**

- \_\_\_ 41. frequently anxious
- \_\_\_ 42. frequently depressed
- \_\_\_ 43. frequently angry
- \_\_\_ 44. frequently upset
- \_\_\_ 45. frequently overwhelmed by cancer
- \_\_\_ 46. diff sleep

**Cognitive Problems**

- \_\_\_ 47. diff concentrating
- \_\_\_ 48. diff remembering
- \_\_\_ 49. diff thinking clearly

**Difficulty Communicat with Friends/Relatives**

- \_\_\_ 50. diff tell fmd/rel to come less often
- \_\_\_ 51. diff tell fmd/rel to leave when not well
- \_\_\_ 52. diff ask fmd/rel to do fun things
- \_\_\_ 53. don't know what to say to fmd/rel
- \_\_\_ 54. diff ask fmd/rel help
- \_\_\_ 55. diff tell fmd/rel about cancer
- \_\_\_ 56. diff ask fmd/rel to come more

**Friends/Relatives Difficulty Interacting**

- \_\_\_ 57. fmd/rel say look well when not
- \_\_\_ 58. fmd/rel withhold information
- \_\_\_ 59. fmd/rel avoid talk cancer
- \_\_\_ 60. fmd/rel do not visit enough
- \_\_\_ 61. fmd/rel do not call enough
- \_\_\_ 62. fmd/rel uncomfor visiting
- \_\_\_ 63. fmd/rel diff talk about cancer

**Anxiety in Medical Situations**

- \_\_\_ 64. uncomfor see patients get treat
- \_\_\_ 65. nervous going to hospital
- \_\_\_ 66. nervous wait to see doctor
- \_\_\_ 67. nervous wait for test results
- \_\_\_ 68. nervous have diagnostic tests
- \_\_\_ 69. nervous get blood drawn

**Worry**

- \_\_\_ 70. worry whether treatments work
- \_\_\_ 71. worry whether cancer progress
- \_\_\_ 72. worry not able to care for self
- \_\_\_ 73. worry how family will manage

**\*Interaction with Children**

- \_\_\_ 89. diff care for child/grandchild
- \_\_\_ 90. diff help children cope
- \_\_\_ 91. diff help children talk about illness

**\*At Work Concerns**

- \_\_\_ 92. diff talk boss about cancer
- \_\_\_ 93. diff talk people at work
- \_\_\_ 94. diff tell employer cannot do work
- \_\_\_ 95. diff ask time off for treatments
- \_\_\_ 96. worried about being fired
- \_\_\_ SUM \_\_\_ # (1-4) 44, 41, 39, 36
- \_\_\_ # Potential Circle

**SEXUAL**

**Sex Interest**

- \_\_\_ 74. doesn't feel sex. attract
- \_\_\_ 75. thinks not sexually attractive to partner(s)
- \_\_\_ 76. not interested in having sex
- \_\_\_ 77. doesn't think partner(s) interested in sex

**\*Sexual Dysfunction**

- \_\_\_ 99. frequency of sex decreased
- \_\_\_ 100. diff become sexually aroused
- \_\_\_ 101. diff with erection (males)
- \_\_\_ 101. diff lubrication (females)
- \_\_\_ 102. diff reach orgasm
- \_\_\_ SUM \_\_\_ # (1-4) 8, 4
- \_\_\_ # Potential Circle

\* Items may not apply to all patients

**MISCELLANEOUS**

**Compliance**

- \_\_\_ 78. doesn't show for MD appoint
- \_\_\_ 79. doesn't show for treatments
- \_\_\_ 80. doesn't take medication
- \_\_\_ 81. doesn't follow MD's instruct
- \_\_\_ SUM \_\_\_ # (1-4) 4 # Potential

**Economic Barriers**

- \_\_\_ 82. financial problems
- \_\_\_ 83. insurance problems
- \_\_\_ 97. diff find new job\*\*
- \_\_\_ 98. employers no hire CA hist\*\*
- \_\_\_ SUM \_\_\_ # (1-4) 4, 2
- \_\_\_ # Potential Circle

**\*Dating**

- \_\_\_ 121. diff initiating dates
- \_\_\_ 122. diff meet dates
- \_\_\_ 123. afraid go places meet dates
- \_\_\_ 124. diff tell date about cancer
- \_\_\_ 125. afraid to initiate sex relation
- \_\_\_ SUM \_\_\_ # (1-4) 5, 0
- \_\_\_ # Potential Circle

**\*Chemotherapy-Related Problems**

- \_\_\_ 126. nervous get chemo
- \_\_\_ 127. nauseated during/before chemo
- \_\_\_ 128. vomit during/before chemo
- \_\_\_ 129. sick when think about chemo
- \_\_\_ 130. nauseated after chemo
- \_\_\_ 131. vomit after chemo
- \_\_\_ 132. tired after chemo
- \_\_\_ 133. other side effects chemo
- \_\_\_ 134. lost hair/grow slow from chemo
- \_\_\_ SUM \_\_\_ # (1-4) 9, 0
- \_\_\_ # Potential Circle

**\*Radiation-Related Problems**

- \_\_\_ 135. fatigued after rad
- \_\_\_ 136. nervous get rad
- \_\_\_ 137. nauseous/vomit after rad
- \_\_\_ SUM \_\_\_ # (1-4) 3, 0
- \_\_\_ # Potential Circle

**\*Ostomy**

- \_\_\_ 138. problems ostomy care/maint.
- \_\_\_ SUM \_\_\_ # (1-4) 1, 0
- \_\_\_ # Potential Circle

**\*Prosthesis**

- \_\_\_ 139. diff with prosthesis
- \_\_\_ SUM \_\_\_ # (1-4) 1, 0
- \_\_\_ # Potential Circle

**Miscellaneous Items**

- \_\_\_ 84. diff with transport
- \_\_\_ 85. gain too much weight
- \_\_\_ 86. diagnostic proced painful
- \_\_\_ 87. frequent diarrhea
- \_\_\_ 88. poor bladder control
- \_\_\_ SUM \_\_\_ # (1-4) 5 # Potential

**SUM ALL 8 MISCELLANEOUS SUMS ABOVE**

\_\_\_ SUM \_\_\_ # (1-4) \_\_\_ # Potential

**Global and Average Severity for CARES and 5 Subscales**

Scale	SUM	#	#	AVE GLOBAL
		Endor	Poten	Sever
Physical	_____	_____	_____	_____
Psychoso	_____	_____	_____	_____
Med Int	_____	_____	_____	_____
Marital	_____	_____	_____	_____
Sexual	_____	_____	_____	_____
Miscell	_____	_____	_____	_____
CARES	_____	_____	_____	_____

Physical \_\_\_\_\_

Psychoso \_\_\_\_\_

Med Int \_\_\_\_\_

Marital \_\_\_\_\_

Sexual \_\_\_\_\_

Miscell \_\_\_\_\_

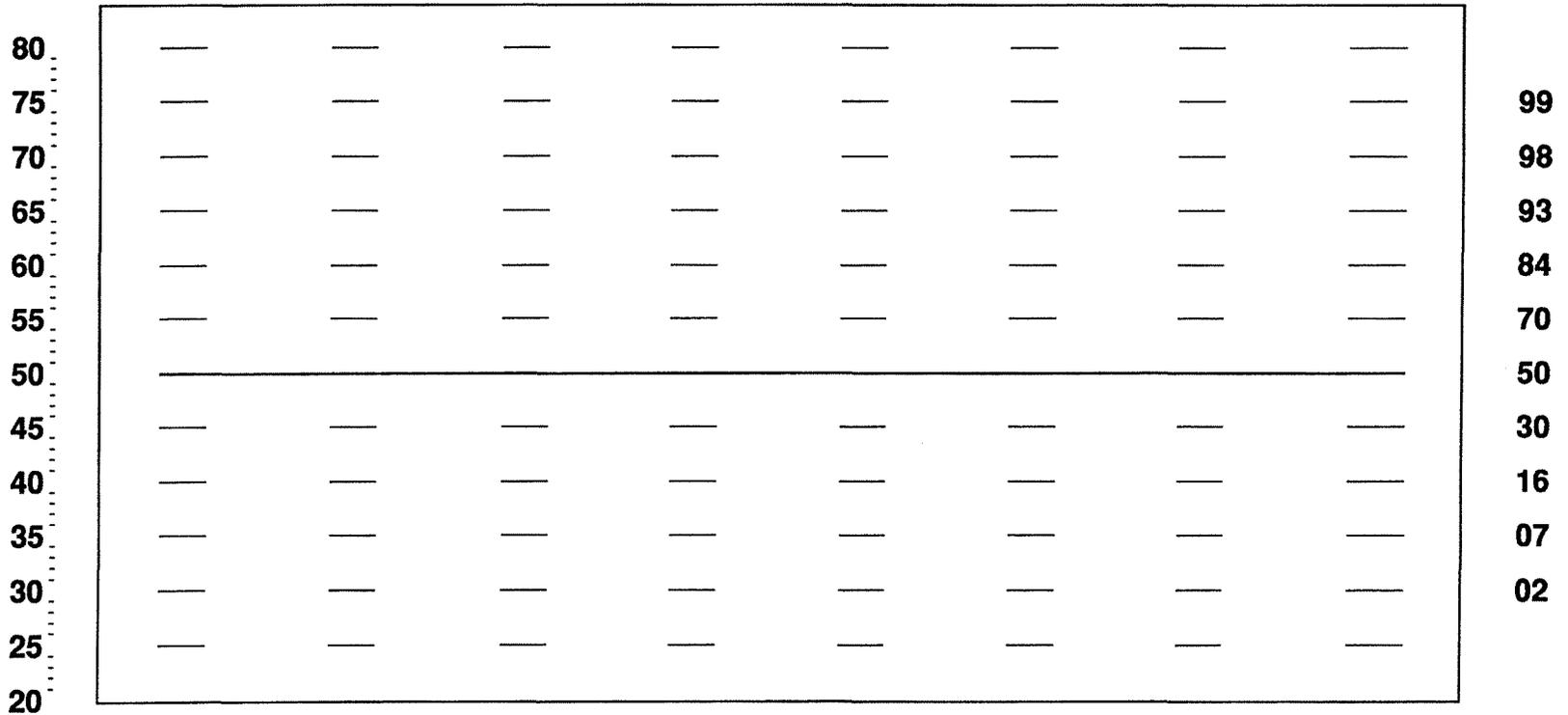
CARES \_\_\_\_\_

## Cancer Rehabilitation Evaluation System (CARES): Patient Profile

<b>Patient Information</b> Name: _____ Date: _____	<b>Please Circle Normative Sample Used:</b> 1. Female Breast Cancer Norm                      4. Male Prostate Cancer Norm 2. Female Other than Breast Cancer Norm        5. Male Other than Prostate Cancer Norm 3. Female Combined Cancer Norm                6. Male Combined Cancer Norm
--	---

**T-Score**

**% Rank**



	CARES Global Score	CARES # Prob Endorsed	CARES Aver Sever	PHYSICAL Global Score	PSYCHOSOCIAL Global Score	MEDICAL INTERACTION Global Score	MARITAL Global Score	SEXUAL Global Score
<b>T</b>								
<b>Raw</b>								

## Bibliography

---

1. Australian Bureau of Statistics. Australia Now - A Statistical Profile: Health; Cancer Control Accessed October, 2000.
2. Australian Bureau of Statistics. *Causes of death, Australia*. ABS Catalogue No. 33003.0 ed. Canberra, 1995.
3. American College of Sports Medicine. *Guidelines for Exercise Testing and Prescription*. 4th ed. Philadelphia: Lea & Febiger, 1991.
4. American College of Sports Medicine. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness in healthy adults. *Medicine and Science in Sports and Exercise*. 22:265-274, 1990.
5. American College of Sports Medicine. *Resource Manual for Guidelines for Exercise Testing and Prescription*. 2nd ed. Philadelphia: Lea & Febiger, 1993.
6. Ades, P. A., M. L. Waldmann, and C. A. Gillespie. A controlled trial of exercise training in older coronary patients. *Journal of Gerontology, Series A, Biological Sciences and Medical Sciences*. 50A:M7-M11, 1995.
7. Ainsworth, B. E., W. L. Haskell, M. C. Whitt, et al. Compendium of physical activities: An update of activity codes and MET intensities. *Medicine and Science in Sports and Exercise*. 32:S498-S516, 2000.
8. Aisenberg, J., K. Hsieh, G. Kalaitzoglou, et al. Bone mineral density in young adult survivors of childhood cancer. *Journal of Pediatric Haematology/Oncology*. 20:241-245, 1998.
9. Aloia, J. F., A. N. Vaswani, J. K. Yeh, and S. H. Cohn. Premenopausal bone mass is related to physical activity. *Archives of Internal Medicine*. 148:121-123, 1988.
10. Andrianopoulos, G., R. L. Nelson, C. T. Bombeck, and G. Souza. The influence of physical activity in 1-2 dimethylhydrazine induced colon carcinogenesis in the rat. *Anticancer Research*. 7:849-852, 1987.
11. Andrykowski, M. A., E. M. Altmaier, R. L. Barnett, et al. The quality of life in adult survivors of allogeneic bone marrow transplantation. *Transplantation*. 50:399-406, 1990.
12. Andrykowski, M. A., M. J. Brady, and P. J. Henslee-Downey. Psychosocial factors predictive of survival after allogeneic bone marrow transplantation for leukaemia. *Psychosomatic Medicine*. 56:342-439, 1994.

## Bibliography

13. Andrykowski, M. A., C. B. Breiner, and E. M. Altmaier. Quality of life following bone marrow transplantation: Findings from a multicentric study. *British Journal of Cancer*. 71:1322-1329, 1995.
14. Andrykowski, M. A., S. Bruehl, M. J. Brady, and P. J. Henslee-Downey. Physical and psychosocial status of adults one-year after bone marrow transplantation: A prospective study. *Bone Marrow Transplantation*. 15:837-844, 1995.
15. Arikoski, P., J. Komulainen, P. Riikonen, J. S. Jurvelin, R. Voutilainen, and H. Kroger. Reduced bone density at completion of chemotherapy for a malignancy. *Archives of Diseases in Childhood*. 80:143-148, 1999.
16. Arikoski, P., J. Komulainen, P. Riikonen, et al. Impaired development of bone mineral density during chemotherapy: A prospective analysis of 46 children newly diagnosed with cancer. *Journal of Bone Mineral Research*. 14:2002-2009, 1999.
17. Arikoski, P., J. Komulainen, P. Riikonen, et al. Alterations in bone turnover and impaired development of bone mineral density in newly diagnosed children with cancer: A 1-year prospective study. *Journal of Clinical Endocrinology and Metabolism*. 84:3174-3181, 1999.
18. Armitage, J. O. Bone marrow transplantation. *New England Journal of Medicine*. 33:827-838, 1994.
19. Arnaud, S. B., D. J. Sherrard, N. Maloney, et al. Effects of 1-week head-down tilt bed rest on bone formation and the calcium endocrine system. *Aviation Space Environmental Medicine*. 63:14-20, 1992.
20. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines. *Journal of Clinical Oncology*. 12:2471-2508, 1994.
21. Avis, N. E., K. W. Smith, R. K. Hambleton, et al. Development of the multidimensional index of life quality: A quality of life measure for cardiovascular disease. *Medical Care*. 34:1102-1120, 1996.
22. Baker, C. A functional status scale for measuring quality of life outcomes in head and neck cancer patients. *Cancer Nursing*. 18:452-457, 1995.
23. Ballard-Barbash, R., A. Schatzkin, and D. Albanes. Physical activity and risk of large bowel cancer in the Framingham study. *Cancer Research*. 50:3610-3613, 1990.
24. Baracos, V. E. Exercise inhibits progressive growth of the Morris hepatoma 7777 in male and female rats. *Canadian Journal of Physiology, Pharmacology*. 67:864-870, 1989.

25. Battista, R. N. and M. J. Hodge. Quality of life research and health technology assessment - a time for synergy. *Quality of Life Research*. 5:413-418, 1996.
26. Beeken, L. and F. Calman. A return to 'normal eating' after curative treatment for oral cancer. What are the long-term prospects? *Oral Oncology, European Journal of Cancer*. 30B:387-392, 1994.
27. Behnke, A. R. and J. H. Wilmore. *Evaluation and Regulation of Body Fluid and Composition*. Englewood Cliffs, New Jersey: Prentice-Hall, 1974.
28. Berk, L. S., K. Nieman, and S. A. Tan. Lymphocyte subset changes during acute maximal exercise. *Medicine and Science in Sports and Exercise*. 18:706, 1986.
29. Berstein, L., B. E. Henderson, R. Hanisch, et al. Physical exercise and breast cancer in young women. *Clinical Journal of Sports Medicine*. 5:144, 1995.
30. Berstein, L., R. K. Ross, and B. E. Henderson. Prospects for the primary prevention of breast cancer. *American Journal of Epidemiology*. 135:142-152, 1992.
31. Beutler, B. and A. Cerami. Cachectin: More than a tumor necrosis factor. *New England Journal of Medicine*. 316:379-386, 1987.
32. Biewener, A. A. and J. E. A. Bertram. Structural response of growing bone to exercise and disuse. *Journal of Applied Physiology*. 76:946-955, 1994.
33. Bijnen, F. C. H., C. J. Caspersen, and W. L. Mosterd. Physical inactivity as a risk factor for coronary heart disease: A WHO and International Society and Federation of Cardiology position statement. *Bulletin of the World Health Organisation*. 72:1-4, 1994.
34. Birk, T. J. HIV and Exercise. *Exercise Immunology Review*. 2:84-95, 1996.
35. Birk, T. J. and C. A. Birk. Use of ratings of perceived exertion for exercise prescription. *Sports Medicine*. 4:1-8, 1987.
36. Bjordal, K., A. Mastekaasa, and S. Kaasa. Self-reported satisfaction with life and physical health in long-term cancer survivors and a matched control group. *Oral Oncology, European Journal of Cancer*. 31B:340-345, 1995.
37. Blaak, E. E., K. R. Westerterp, O. Bar-Or, et al. Total energy expenditure and spontaneous activity in relation to training in obese boys. *American Journal of Clinical Nutrition*. 55:777-782, 1992.
38. Black, P., P. Gutjahr, and H. Stopfkuchen. Physical performance in long-term survivors of acute leukaemia in childhood. *European Journal of Pediatrics*. 157:464-467, 1998.

## Bibliography

39. Blair, S., H. W. Kohl, and R. S. Paffenbarger. Physical fitness and all-cause mortality: A prospective study of healthy men and women. *Journal of the American Association*. 262:2395-2401, 1989.
40. Bland, J. M. and D. G. Altman. Statistical methods for assessing agreement between two methods of clinical measurement. *The Lancet*. February 8:307-310, 1986.
41. Blesch, K. S. Rehabilitation of the cancer patient at home. *Seminars in Oncology Nursing*. 12:219-225, 1996.
42. Bloch, R. *Bloch's Manuscript. Self help Exercises*. Chapter 7. 1994.
43. Blomgren, H., E. Baral, F. Esmyr, et al. Natural killer activity in peripheral lymphocyte population following local radiation therapy. *Acta Radiology Oncology*. 19:139-143, 1980.
44. Bloom, B. R. In vitro approach to the mechanism of cell-mediated immune reactions. *Advanced Immunology*. 13, 1971.
45. Bloomfield, S. M., W. J. Mysiw, and R. D. Jackson. Bone mass and endocrine adaptations to training in spinal cord injured individuals. *Bone*. 19:61-68, 1996.
46. Body, J. J., J. C. Dumon, E. Gineyts, and P. D. Delmas. Comparative evaluation of markers of bone resorption in patients with breast cancer-induced osteolysis before and after bisphosphonate therapy. *British Journal of Cancer*. 75:408-412, 1997.
47. Bonavida, B. and S. C. Wright. Multistage model of natural killer cell mediated cytotoxicity involving NKCF as soluble cytotoxic mediators. *Advanced Cancer Research*. 49:169-187, 1987.
48. Borg, G. A. V. Psychological bases of physical exertion. *Medicine and Science in Sports and Exercise*. 14:377-381, 1982.
49. Bouchard, C. and J-P. Despres. Physical activity and health: Atherosclerotic, metabolic and hypertensive diseases. *Research Quarterly for Exercise and Sport*. 66:268-275, 1995.
50. Brennan, M. J., R. W. De Pompolo, and F. H. Garden. Cardiovascular, pulmonary, and cancer rehabilitation. 3. Cancer rehabilitation. *Archives of Physical Medicine and Rehabilitation*. 77:S52-S65, 1996.
51. Brenner, B. G., C. Vo, and M. A. Wainberg. Different effects of breast cancer, HIV-1 infection and chemotherapy on inducible natural immunity. S183-S185, 1991.
52. Brill, P. A., C. A. Macera, D. R. Davis, et al. Muscular strength and physical function. *Medicine and Science in Sports and Exercise*. 32:412-416, 2000.

53. Brittenden, J., S. D. Heys, J. Ross, and O. Eremin. Natural killer cells and cancer. *Cancer*. 77:1226-1246, 1996.
54. Brownson, R. C., S. H. Zahm, and J. C. Chang. Occupational risk of colon cancer. *American Journal of Epidemiology*. 130:675-687, 1991.
55. Buchfuhrer, M. J., J. E. Hansen, T. E. Robinson, D. Y. Sue, K. Wasserman, and B. M. Whipp. Optimizing the exercise protocol for cardiopulmonary assessment. *Journal of Applied Physiology*. 55:1558-1564, 1983.
56. Busschbach, J. J. V., P. E. Horikx, J. M. M. van den Bosch, et al. Measuring the quality of life before and after bilateral lung transplantation in patients with cystic fibrosis. *Chest*. 105:911-917, 1994.
57. Butterfield, G. E. and D. H. Calloway. Physical activity improves protein utilisation in young men. *British Journal of Nutrition*. 51:171-187, 1984.
58. Calzolari, A., C. Baronci, G. Biondi, et al. Evaluation of a group of leukaemic children 'off-therapy' towards their inclusion in physical activities. *Journal of Sports Cardiology*. 2:108-115, 1985.
59. Canales, S., P. A. Ganz, and C. A. Coscarelli. Translation and validation of a quality of life instrument for Hispanic American cancer patients: Methodological considerations. *Quality of Life Research*. 4:3-11, 1995.
60. Carbon, R. J. Exercise, amenorrhoea and the skeleton. *British Medical Bulletin*. 48:546-560, 1992.
61. Carlson, K., B. Simonsson, and S. Ljunghall. Acute effects of high-dose chemotherapy followed by bone marrow transplantation on serum markers of bone metabolism. *Calcified Tissue International*. 55:408-411, 1994.
62. Carpenter, W. H., E. T. Poehlman, M. O'Connell, and M. I. Goran. Influence of body composition and resting metabolic rate on variation in total energy expenditure: A meta-analysis. *American Journal of Clinical Nutrition*. 61:4-10, 1995.
63. Caspersen, C. J., M. A. Pereira, and K. M. Curran. Changes in physical activity patterns in the United States, by sex and cross-sectional age. *Medicine and Science in Sports and Exercise*. 32:1601-1609, 2000.
64. Castaneda, S., L. Carmona, I. Carvajal, et al. Reduction of bone mass in women after bone marrow transplantation. *Calcified Tissue International*. 60:343-347, 1997.
65. Cella, D. F. Methods and problems in measuring quality of life. *Support Care Cancer*. 3:11-22, 1995.

## Bibliography

66. Chan, G. M., M. McMurry, K. Westover, et al. Effects of increased dietary calcium intake upon the calcium and bone mineral status of lactating adolescent and adult women. *American Journal of Clinical Nutrition*. 46:319-323, 1987.
67. Chapman, K. M. and R. A. Nelson. Loss of appetite: Managing unwanted weight loss in the older patient. *Geriatrics*. 49:54-59, 1994.
68. Charuhas, P. M., K. Rosenberg, B. Bruemmer, et al. A double-blind randomized trial comparing outpatient parenteral nutrition with intravenous hydration effect on resumption of oral intake after marrow transplantation. *Journal of Parenteral and Enteral Nutrition*. 21:157-161, 1997.
69. Chaturvedi, S. K., P. S. Chandra, S. M. Channabasavanna, et al. Levels of anxiety and depression in patients receiving radiotherapy in India. *Psycho-Oncology*. 5:343-346, 1996.
70. Chess, L., R. P. McDermott, and S. I. Schlossman. Immunologic function of isolated human lymphocyte subpopulations. I. Quantitative isolation of human T & B cells and response to mitogen. *Journal of Immunology*. 113:113-1121, 1974.
71. Cohen, S., D. A. J. Tyrrell, and A. P. Smith. Psychological stress and susceptibility to the common cold. *The New England Journal of Medicine*. 325:606-612, 1991.
72. Cohen, S. R., S. A. Hassa, B. J. Lapointe, and B. M. Mount. Quality of life in HIV disease as measured by the McGill quality of life questionnaire. *AIDS*. 10:1421-1427, 1996.
73. Cohen, S. R., B. M. Mount, J. J. N. Tomas, and L. F. Mount. Existential well-being is an important determinant of quality of life. *Cancer*. 77:576-586, 1996.
74. Cole, T. J. and W. A. Coward. Precision and accuracy of doubly labeled water energy expenditure by multipoint and two-point methods. *American Journal of Physiology*. 263:E965-E973, 1992.
75. Corner, J., H. Plant, A. A'Hern, and C. Bailey. Non-pharmacological intervention for breathlessness in lung cancer. *Palliative Medicine*. 10:299-305, 1996.
76. Coscarelli, A. and R. L. Heinrich. *Cancer Rehabilitation Evaluation System - CARES - Manual*. Santa Monica, CA, 1988.
77. Courneya, K. S. and C. M. Friedenreich. Physical exercise and quality of life following cancer diagnosis: A literature review. *Annals of Behavioral Medicine*. 21:171-179, 1999.

78. Courneya, K. S. and C. M. Friedenreich. Relationship between exercise pattern across the cancer experience and current quality of life in colorectal cancer survivors. *The Journal of Alternative and Complementary Medicine*. 3:215-226, 1997.
79. Courneya, K. S. and C. M. Friedenreich. Utility of the theory of planned behaviour for understanding exercise during breast cancer treatment. *Psycho-Oncology*. 8, 1999.
80. Courneya, K. S., M. R. Keats, and R. A. Turner. Physical exercise and quality of life in cancer patients following high dose chemotherapy and autologous bone marrow transplantation. *Psycho-Oncology*. 9:127-136, 2000.
81. Crilley, P. and L. J. Goldstein. Peripheral blood stem cell transplant in breast cancer. *Seminars in Oncology*. 22:238-249, 1995.
82. Croarkin, E. Osteopenia in the patient with cancer. *Physical Therapy*. 79:196-201, 1999.
83. Cummings, S. R., D. M. Black, M. C. Nevitt, et al. Bone density at various sites for prediction of hip fractures. *Lancet*. 341:72-75, 1993.
84. Cunningham-Rundles, S., D. A. Filippa, D. W. Braun, et al. Natural cytotoxicity of peripheral blood lymphocytes and regional lymph node cells of breast cancer in women. *Journal of the National Cancer Institute*. 67:585-590, 1981.
85. Curbow, B., M. R. Somerfield, F. Baker, et al. Personal changes, dispositional optimism, and psychological adjustment to bone marrow transplantation. *Journal of Behavioral Medicine*. 16:423-443, 1993.
86. Dafoe, W. and P. Huston. Current trends in cardiac rehabilitation. *Canadian Medical Association Journal*. 156:527-532, 1997.
87. Dalsky, G. P., K. S. Stocke, A. A. Ehsani, et al. Weight-bearing exercise training and lumbar bone in postmenopausal women. *Annals of Internal Medicine*. 108:824-828, 1988.
88. Davies, P. S. W. Measurement of energy expenditure and body composition using stable isotopes. *Developmental Physiopathology and Clinics*. 2:95-110, 1991.
89. Davies, P. S. W., J. E. Cameron, and A. Lucas. *Reference data for total energy expenditure in early infancy*. Switzerland: EDECG Publication, 1990, 103-116.
90. Davies, P. S. W. and J. C. K. Wells. Calculation of total body water in infancy. *European Journal of Clinical Nutrition*. 48:490-495, 1994.

## Bibliography

91. Davies, P. S. W., J. C. K. Wells, and A. Lucas. Adjusting milk intake for body size in early infancy. *Early Human Development*. 36:61-67, 1994.
92. Davis, R. L., P. R. Cavanagh, H. J. Sommer, and G. Wu. Ground reaction forces during locomotion in simulated microgravity. *Aviation, Space and Environmental Medicine*. 67:235-242, 1996.
93. Delmas, P. D. Biochemical markers of bone turnover for the clinical investigation of osteoporosis. *Osteoporosis International*. Suppl 1:S81-S86, 1993.
94. Demark-Wahnefried, W., V. Hars, M. R. Conaway, et al. Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. *American Journal of Clinical Nutrition*. 65:1495-1501, 1997.
95. Demark-Wahnefried, W., B. Peterson, C. McBride, et al. Current health behaviors and readiness to pursue life-style changes among men and women diagnosed with early stage prostate and breast carcinomas. *Cancer*. 88:674-684, 2000.
96. Demark-Wahnefried, W., E. P. Winer, and B. K. Rimer. Why women gain weight with adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology*. 11:1418-1429, 1993.
97. de Schepper, J., S. Hachimi-Idrissi, O. Louis, et al. Bone metabolism and mineralisation after cytotoxic chemotherapy including ifosfamide. *Archives of Diseases in Childhood*. 71:346-348, 1994.
98. Deuster, P. A., S. D. Morrison, and R. A. Ahrens. Endurance exercise modifies cachexia of tumor growth in rats. *Medicine and Science in Sports and Exercise*. 17:385-392, 1985.
99. De Wys, W. D., C. Begg, and P. T. Lavin. Prognostic effect of weight loss prior to chemotherapy in cancer patients. *American Journal of Medicine*. 69:491-497, 1980.
100. Dietz, J. H. *Rehabilitation and physical medicine*. Chicago: American College of Surgeons, 1970.
101. Dimeo, F., H. Bertz, J. Finke, et al. An aerobic exercise program for patients with haematological malignancies after bone marrow transplantation. *Bone Marrow Transplantation*. 18:1157-1160, 1996.
102. Dimeo, F., S. Fetscher, W. Lange, et al. Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. *Blood*. 18:1157-1160, 1997.

103. Dimeo, F., B. G. Rumberger, and J. Keul. Aerobic exercise as therapy for cancer fatigue. *Medicine and Science in Sports and Exercise*. 30:475-478, 1998.
104. Dimeo, F., M. H. M. Tilmann, H. Bertz, et al. Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. *Cancer*. 79:1717-1722, 1997.
105. Dimeo, F. C., R-D. Stieglitz, U. Novelli-Fischer, et al. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. *Cancer*. 15:2273-2277, 1999.
106. Down, J. D. and R. E. Ploemacher. Transient and permanent engraftment potential of murine hematopoietic stem cell subsets: Differential effects of host conditioning with gamma radiation and cytotoxic drugs. *Experimental Hematology*. 21:913-921, 1993.
107. Dudas, A. and C. Carlson. Cancer rehabilitation. *Oncology Nursing Forum*. 15:183-188, 1988.
108. Dudrick, S. J., B. V. MacFadyen, E. A. Souchon, et al. Parenteral nutrition techniques in cancer patients. *Cancer Research*. 37:2440-2450, 1977.
109. Eames, G. M., J. Crosson, J. Steinberger, et al. Cardiovascular function in children following bone marrow transplant - A cross-sectional study. *Bone Marrow Transplantation*. 19:61-66, 1997.
110. Eichner, E. R. Exercise, lymphokines, calories, and cancer. *The Physician and Sportsmedicine*. 15:109-115, 1987.
111. Epstein, J. H. How I manage sunburn. *The Physician and Sportsmedicine*. 13:81-85, 1985.
112. Epstein, O. Serum and urinary markers of bone remodeling: Assessment of bone turnover. *Endocrine Reviews*. 9:437-449, 1988.
113. Eriksen, E. F., D. W. Axelrod, and F. Melsen. *Bone Histomorphometry*. New York: Raven Press, 1994, p13-15.
114. Fagard, R. and C. Tipton. *Physical activity, fitness and hypertension*. Champaign: Human Kinetics Publishers, 1993.
115. Falconer, J. S., K. C. H. Fearon, C. E. Plester, et al. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. *Annals of Surgery*. 219:325-331, 1994.
116. Fehily, A. M., R. J. Coles, W. D. Evans, and P. C. Elwood. Factors affecting bone density in young adults. *American Journal of Clinical Nutrition*. 56:579-586, 1992.

## Bibliography

117. Feigenbaum, M. S. and M. L. Pollock. Strength training: Rationale for current guidelines for adult fitness programs. *The Physician and Sportsmedicine*, 1997.
118. Feld, R. Endpoints in cancer clinical trials: Is there a need for measuring quality of life? *Support Care Cancer*. 3:23-37, 1995.
119. Fletcher, G. F., G. Balady, S. N. Blair, et al. Statement on exercise: Benefits and recommendation for physical activity for all Americans - A statement for Health Professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 94:857-862, 1996.
120. Fletcher, G. F., S. N. Blair, and J. Blumenthal. AHA Medical/Scientific Statement - Statement of exercise - Benefits and recommendations for physical activity programs for all Americans - A statement for Health Professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 86:340-344, 1992.
121. Fow, N. R. Cancer rehabilitation: An investment in survivorship. *Rehabilitation Management*. April/May:48-53, 1996.
122. Fredriksson, M., N. O. Bengtsson, L. Hardell, and O. Axelson. Colon cancer, physical activity, and occupational exposures - A case control study. *Cancer*. 63:1838-1842, 1989.
123. Fredrix, E. W. H. M., A. J. Staal van den Brekel, and E. F. M. Wouters. Energy balance in non-small cell lung carcinoma patients before and after surgical resection of their tumors. *Cancer*. 79:717-723, 1997.
124. Friedenreich, C. M. and K. S. Courneya. Exercise as rehabilitation for cancer patients. *Clinical Journal of Sport Medicine*. 6:237-244, 1996.
125. Frisch, R. E., G. Wyshak, N. L. Albright, et al. Lower prevalence of non-reproductive system cancers among female former college athletes. *Medicine and Science in Sports and Exercise*. 21:250-253, 1989.
126. Gale, R. P., J. O. Armitage, and K. A. Dicke. Autotransplants: Now and in the future. *Bone Marrow Transplant*. 7:153-157, 1991.
127. Galun, E., R. Burstein, E. Assia, et al. Changes of white blood cell count during prolonged exercise. *International Journal of Sports Medicine*. 8:253-255, 1987.
128. Gammon, M. D. and E. M. John. Recent etiologic hypotheses concerning breast cancer. *Epidemiology Reviews*. 15:163-168, 1993.
129. Ganz, P. A. Current issues in cancer rehabilitation. *Cancer*. 65:742-751, 1990.

130. Ganz, P. A. Quality of life and the patient with cancer - Individual and policy implications. *Cancer*. 15:1445-1152, 1994.
131. Ganz, P. A., K. Hirji, M-S. Sim, et al. Predicting psychosocial risk in patients with breast cancer. *Medical Care*. 31:419-431, 1993.
132. Ganz, P. A., C. A. C. Schag, J. J. Lee, and M-S. Sim. The CARES: A generic measure of health-related quality of life for patients with cancer. *Quality of Life Research*. 1:19-29, 1992.
133. Gauthier, M. M. Can exercise reduce the risk of cancer? *The Physician and Sportsmedicine*. 14:171-178, 1986.
134. Gerhardsson, D. E., M. Verdier, and G. Steineck. Physical activity and colon cancer: A case-referent study in Stockholm. *British Journal of Cancer*. 46:985-989, 1990.
135. Giacosa, A., F. Frascio, S. G. Sukkar, and S. Roncella. Food intake and body composition in cancer cachexia. *Nutrition*. 12:S20-S23, 1996.
136. Giannini, S., M. Nobile, L. Sartori, et al. Bone density and mineral metabolism in thyroidectomized patients treated with long-term L-thyroxine. *Clinical Science*. 87:593-597, 1994.
137. Gilbert, C. J. Peripheral blood progenitor cell transplantation for breast cancer: Pharmacoeconomic considerations. *Pharmacotherapy*. 16:S101-S108, 1996.
138. Gilsanz, V., M. E. Carlson, T. F. Roe, and J. A. Ortega. Osteoporosis after cranial irradiation for acute lymphoblastic leukaemia. *Journal of Pediatrics*. 117:238-244, 1990.
139. Given, C. W., B. Given, F. Azzouz, et al. Comparison of changes in physical functioning of elderly patients with new diagnoses of cancer. *Medical Care*. 38:482-493, 2000.
140. Goerres, G., A. Kaim, A. Ottes, et al. Bone mineral density in patients receiving suppressive doses of thyroxine for differentiated thyroid carcinoma. *European Journal of Nuclear Medicine*. 23:690-692, 1996.
141. Goerres, G., R. Theiler, and J. Muller-Brand. Interfemur variation of bone mineral density in patients receiving high-dose thyroxine therapy. *Calcified Tissue International*. 63:98-101, 1998.
142. Goran, M. I. Variation in total energy expenditure in humans. *Obesity Research*. 3:59-66, 1995.

## Bibliography

143. Goran, M. I. and E. T. Poehlman. Total energy expenditure and energy requirements in healthy elderly persons. *Metabolism*. 41:744-753, 1992.
144. Gore, C. J. and D. A. Edwards. *Australian Fitness Norms: A Manual for Fitness Assessors*. South Australia: The Health Development Foundation, 1992
145. Gotay, C. C., E. L. Korn, M. S. McCabe, et al. Quality-of-life assessment in cancer treatment protocols: Research issues in protocol development. *Journal of the National Cancer Institute*. 84:575-579, 1992.
146. Gray, B. Exercise and the human immune system. *EXCEL*. 6:12-14, 1990.
147. Greenlee, R. T., M. B. Hill-Harmon, T. Murray, and M. Thun. Cancer statistics, 2001. *CA: A Cancer Journal for Clinicians*. 51:15-38, 2001.
148. Greenlee, R. T., T. Murray, S. Bolden, and P. A. Wingo. Cancer statistics, 2000. *CA - A Cancer Journal for Clinicians*. 50:7-33, 2000.
149. Grossarch-Maticek, R., H. J. Eysenck, G. Uhlenbruck, et al. Sport activity and personality as elements in preventing cancer and coronary heart disease. *Perceptual and Motor Skills*. 71:199-209, 1990.
150. Grosvenor, M., L. Bulcavage, and R. T. Chlebowski. Symptoms potentially influencing weight loss in a cancer population. *Cancer*. 63:330, 1989.
151. Hanke, C. W., T. W. Zollinger, J. J. O'Brian, and L. Bianco. Skin cancer in professional and amateur female golfers. *Physician and Sportsmedicine*. 13:51-77, 1985.
152. Hannel, I., F. Erkeller-Yuksel, V. Deneys, et al. Lymphocyte populations as a function of age. *Immunology Today*. 13:215-218, 1992.
153. Hansson, L. I., A. Stenstrom, and K. G. Thorngren. Development of osteopenia in the 4th lumbar vertebra during prolonged bed rest after operation for scoliosis. *Acta Orthopaedica Scandinavica*. 46:621-630, 1975.
154. Harvey, R. F., H. M. Jellinek, and R. V. Habeck. Cancer rehabilitation: An analysis of 36 program approaches. *Journal of the American Medical Association*. 247:2127-2131, 1982.
155. Hassey Dow, K. A review of late effects of cancer in women. *Seminars in Oncology Nursing*. 11:128-136, 1995.
156. Henderson, R. C., C. D. Madsen, C. Davis, and S. H. Gold. Bone density in survivors of childhood malignancies. *Journal of Pediatric Hematology/Oncology*. 18:367-371, 1996.

157. Henderson, R. C., C. D. Madsen, C. Davis, and S. H. Gold. Longitudinal evaluation of bone mineral density in children receiving chemotherapy. *Journal of Pediatric Haematology/Oncology*. 20:322-326, 1998.
158. Henon, P. R., H. Liang, G. Beck-Wirth, et al. Comparison of hematopoietic and immune recovery after autologous bone marrow or stem cell transplants. *Bone Marrow Transplant*. 9:285-291, 1992.
159. Hesseling, P. B., S. F. Hough, E. D. Nel, et al. Bone mineral density in long-term survivors of childhood cancer. *International Journal of Cancer*. 11:44-47, 1998.
160. Hettinger, T. *Physiology of Strength*. Springfield: Charles C Thomas, 1961.
161. Hicks, J. E. *Exercise for Cancer Patients*. Baltimore: Williams & Wilkins, 1990.
162. Hill, M. J. Physical activity and human cancer. *European Journal of Cancer Prevention*. 8:475-477, 1999.
163. Hirose, K., K. Tajima, N. Hamajima, et al. A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. *Japanese Journal of Cancer Research*. 86:146-154, 1995.
164. Hoffmam-Goetz, L., J. R. Simon, and N. Cipp. Lymphocyte subset responses to repeated submaximal exercise in men. *Journal of Applied Physiology*. 68:1069-1074, 1990.
165. Hoffman-Goetz, L. Exercise, natural immunity, and tumor metastasis. *Medicine and Science in Sports and Exercise*. 26:157-163, 1994.
166. Hogarty, A. N., A. Leabey, H. Zhao, et al. Longitudinal evaluation of cardiopulmonary performance during exercise after bone marrow transplantation in children. *The Journal of Pediatrics*. 136:311-317, 2000.
167. Houde, J. P., L. A. Schulz, and W. J. Morgan. Bone mineral density changes in the forearm after immobilisation. *Clinical Orthopaedics and Related Research*:199-205, 1995.
168. Hunter, M. Rehabilitation in cancer care: A patient-focused approach. *European Journal of Cancer Care*. 7:85-87, 1998.
169. Hyland, M. E. Quality-of-life measures as providers of information on value-for-money of health interventions. *PharmacoEconomics*. 11:19-31, 1997.
170. Inui, A. Cancer anorexia-cachexia syndrome: Are neuropeptides the key? *Cancer Research*. 59:4493-4501, 1999.

## Bibliography

171. Irvine, D. M., L. Vincent, N. Bubela, et al. A critical appraisal of the research literature investigating fatigue in the individual with cancer. *Cancer Nursing*. 14:188-199, 1991.
172. Irvine, E. J. Measuring quality of life: A review. *Scandinavian Journal of Gastroenterology*. 31:5-7, 1996.
173. Irwin, M., M. Daniel, S. C. Risch, et al. Plasma cortisol and natural killer cell activity during bereavement. *Biological Psychiatry*. 24:173-178, 1988.
174. Jackson, A. S. and M. L. Pollock. Practical assessment of body composition. *The Physician and Sportsmedicine*. 13:76-90, 1985.
175. Jankovic, M., P. Brouwers, M. G. Valsecchi, et al. Association of 1800 cGy cranial irradiation with intellectual function in children with acute lymphoblastic leukaemia. *Lancet*. 344:224-227, 1994.
176. Jaworski, Z. F. and H. K. Uthoff. Reversibility of non-traumatic disuse osteoporosis during its active phase. *Bone*. 7:431-439, 1986.
177. Jebb, S. A. Energy metabolism in cancer and human immunodeficiency virus infection. *Proceedings of the Nutrition Society*. 56:763-775, 1997.
178. Jebb, S. A., R. J. Osborne, A. K. Dixon, et al. Measurements of resting energy expenditure and body composition before and after treatment of small cell lung cancer. *Annals of Oncology*. 5:915-919, 1994.
179. Jelfs, P., M. Coates, and G. Giles. *Cancer in Australia 1989-1990 (with projections to 1995)*. Canberra: Australasian Association of Cancer Registries, 1995.
180. Jenney, M. E. M., E. B. Faragher, P. H. Morris-Jones, and A. Woodcock. Lung function and exercise capacity in survivors of childhood leukaemia. *Medical Paediatric Oncology*. 24:222-230, 1995.
181. Johnson, J. B. and A. W. Kelly. A multifaceted rehabilitation program for women with cancer. *Oncology Nursing Forum*. 17:691-695, 1990.
182. Jones, H. H., J. D. Priest, W. C. Hayes, et al. Humeral hypertrophy in response to exercise. *Journal of Bone and Joints Surgery*. 59A:204-208, 1977.
183. Jones, R. H. *Longitudinal data with serial correlation: A state-space approach*. Bury St Edmunds, Suffolk: Chapman & Hall, 1993.
184. Kandors, B., D. W. Dempster, and R. Lindsay. Interaction of calcium nutrition and physical activity on bone mass in young women. *Journal of Bone and Mineral Research*. 3:145-149, 1988.

185. Kannus, P., L. Jozsa, M. Kvist, et al. Expression of osteocalcin in the patella of experimentally immobilised and remobilised rats. *Journal of Bone and Mineral Research*. 11:79-87, 1996.
186. Kannus, P., H. Sievanen, T. L. N. Jarvinen, et al. Effects of free mobilisation and low- to high- intensity treadmill running on the immobilisation-induced bone loss in rats. *Journal of Bone and Mineral Research*. 9:1613-1619, 1994.
187. Karvonen, J. and T. Vuorimaa. Heart rate and exercise intensity during sports activities: Practical application. *Sports Medicine*. 5:303-312, 1988.
188. Kaste, S. C., R. W. Chesney, M. M. Hudson, et al. Bone mineral status during and after therapy of childhood cancer: An increasing population with multiple risk factors for impaired bone health. *Journal of Bone and Mineral Research*. 14:2010-2014, 1999.
189. Katch, F. I. and W. D. McArdle. *Introduction to Nutrition, Exercise and Health*. Philadelphia: Lea & Febiger, 1993.
190. Kaver, I. T Lymphocyte subsets and function in the peripheral blood of patients with urological cancer. *Oncology*. 49:108-113, 1992.
191. Keast, D., K. Cameron, and A. R. Morton. Exercise and immune response. *Sports Medicine*. 5:248-267, 1988.
192. Keats, M. R., K. S. Courneya, S. Danielsen, and S. F. Whitsett. Leisure-Time Physical Activity and Psychosocial Well-Being in Adolescents After Cancer Diagnosis. *Journal of Pediatric Oncology Nursing*. 16:180-188, 1999.
193. Keilholz, U., R. Max, C. Scheibenbogen, et al. Endocrine function and bone metabolism 5 years after autologous bone marrow/blood-derived progenitor cell transplantation. *Cancer*. 79:1617-1622, 1997.
194. Kent, H. Breast-cancer survivors begin to challenge exercise taboos. *Canadian Medical Association Journal*. 155:969-971, 1996.
195. Keys, A., J. Brozek, O. Henschel, et al. *The Biology of Human Starvation*. Minneapolis: University of Minnesota Press, 1950.
196. Kiecolt-Glaser, J. K., W. Garner, C. E. Speicher, et al. Psychosocial modifiers of immunocompetence in medical students. *Psychosomatic Medicine*. 46:7-14, 1984.
197. Kiecolt-Glaser, J. K., R. Glaser, D. Williger, et al. Psychosocial enhancement of immunocompetence in a geriatric population. *Health Psychology*. 4:25-41, 1985.
198. Koetting, C. A. and G. M. Wardlaw. Wrist, spine and hip bone density in women with variable histories of lactation. *American Journal of Clinical Nutrition*. 48:1479-1481, 1988.

199. Kohl, H. W., R. E. LaPorte, and S. N. Blair. Physical activity and cancer: An epidemiological perspective. *Sports Medicine*. 6:222-237, 1988.
200. Krolner, B. Lumbar spine bone mineral content by photon beam absorptiometry. *Danish Medical Bulletin*. 32:152-175, 1985.
201. Kutynec, C. L., L. McCargar, S. I. Barr, and G. T. Hislop. Energy balance in women with breast cancer during adjuvant treatment. *Journal of the American Dietetic Association*. 99:1222-1227, 1999.
202. Lanyon, L. E. Functional strain in bone tissue as an objective and controlling stimulus for adaptive bone remodeling. *Journal of Biomechanics*. 20:1081-1083, 1987.
203. LaPerriere, A., M. H. Antoni, N. Schneiderman, et al. Exercise intervention attenuates emotional distress and natural killer cell decrements following notification of positive serological status for HIV-1. *Biofeedback Self-Regulation*. 15:229-242, 1990.
204. LaPerriere, A., G. Ironson, M. H. Antoni, et al. Exercise and psychoneuroimmunotherapy. *Medicine and Science in Sports and Exercise*. 26:182-190, 1994.
205. LaPerriere, A., N. Klimas, M. A. Fletcher, et al. Change in CD4+ cell enumeration following aerobic exercise training in HIV-1 disease: Possible mechanisms and practical applications. *International Journal of Sports Medicine*. 18:S56-S61, 1997.
206. Larsen, J., A. Gardulf, G. Nordstrom, et al. Health-related quality of life in women with breast cancer undergoing autologous stem-cell transplantation. *Cancer Nursing*. 19:368-375, 1996.
207. Lawrence, T. S., J. M. Robertson, M. S. Anscher, et al. Hepatic toxicity resulting from cancer treatment. *International Journal of Radiation Oncology, Biology, Physics*. 31:1237-1248, 1995.
208. LeBlanc, A., V. Schneider, E. Spector, et al. Calcium absorption, endogenous excretion and endocrine changes during and after long-term bed rest. *Bone*. 16:301S-304S, 1995.
209. LeBlanc, A. D., V. S. Schneider, and H. J. Evans. Regional changes in muscle mass following 17 weeks of bed rest. *Journal of Applied Physiology*. 73:2172-2178, 1992.
210. Lee, I-M. Exercise and physical health: cancer and immune function. *Research Quarterly for Exercise and Sport*. 66:286-291, 1995.

211. Lee, I-M. and R. S. Paffenbarger. Physical activity and its relation to cancer risk: A prospective study of college alumni. *Medicine and Science in Sports and Exercise*. 26:831-837, 1994.
212. Lee, I. M., R. S. Paffenbarger, and C. C. Hsieh. Physical activity and risk of prostatic cancer among college alumni. *American Journal of Epidemiology*. 135:169-179, 1992.
213. Lehman, A. F. Measuring quality of life in a reformed health system. *Health Affairs*. 14:90-101, 1995.
214. Leslie, W. D., E. A. Cowden, and J. P. Maclean. Oestrogen and bone density: A comparison of tamoxifen and hypo-oestrogenaemia. *Nuclear Medicine Communications*. 16:698-702, 1995.
215. Lewicki, R., H. Tchorzewski, and E. Majewska. Effect of maximal physical exercise on T-lymphocyte subpopulations and on IL-1 and IL-2 production in vitro. *International Journal of Sports Medicine*. 9:114-117, 1988.
216. Liberti, G., R. Pearce, and G. Taghipour. Comparison of peripheral blood stem-cell and autologous bone marrow transplantation for lymphoma patients: A case-controlled analysis of the BMT Registry data. *Annals of Oncology*. 5:5151-5153, 1994.
217. Lin, Y. S. and J. H. I. Chen. The effect of chronic and acute exercise on immunity in rats. *International Journal of Sports Medicine*. 14:86-92, 1993.
218. Lindsay, R. Prevention of osteoporosis. *Preventive Medicine*. 23:722-726, 1994.
219. Lindsay, R., D. M. Hart, C. Forrest, and e. al. Prevention of spinal osteoporosis in oophorectomized women. *Lancet*. 2:199-204, 1980.
220. Liu, S., I-M. Lee, P. Linson, et al. A prospective study of physical activity and risk of prostate cancer in US physicians. *International Journal of Epidemiology*. 29:29-35, 2000.
221. Love, R. R., H. S. Barden, R. B. Mazess, et al. Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. *Archives of Internal Medicine*. 154:2585-2588, 1994.
222. Lox, C. L., E. McAuley, and R. S. Tucker. Aerobic and resistance exercise - training effects on body composition, muscular strength, and cardiovascular fitness in an HIV-1 population. *International Journal of Behavioral Medicine*. 3:55-69, 1996.
223. MacKinnon, L. T., T. W. Chick, A. van As, and T. B. Tomasi. *Effects of prolonged intense exercise on natural killer cell number and function*. New York: AMS Press, 1988, 77-89.

## Bibliography

224. MacKinnon, L. T. and T. B. Tomasi. *Immunology of exercise*. 3rd ed. Baltimore: Urban and Schwarzenberg, 1989, 273-289.
225. MacKinnon, L. T. and T. B. Tomasi. Immunology of exercise. *Annals of Sports Medicine*. 3:1-4, 1986.
226. MacVicar, M. G. and M. L. Winningham. Promoting the functional capacity of cancer patients. *The Cancer Bulletin*. 38:235-239, 1986.
227. MacVicar, M. G., M. L. Winningham, and J. L. Nickel. Effects of aerobic interval training on cancer patients' functional capacity. *Nursing Research*. 38:348-351, 1989.
228. Maines, T. Y., C. J. Lavie, R. V. Milani, et al. Effects of cardiac rehabilitation and exercise programs on exercise capacity, coronary risk factors, behavior and quality of life in patients with coronary artery disease. *Southern Medical Journal*. 90:43-49, 1997.
229. Malik, S. T. A., M. S. Naylor, N. East, et al. Cells secreting tumour necrosis factor show enhanced metastasis in nude mice. *European Journal of Cancer*. 26:1031-1034, 1990.
230. Manolagas, S. C. and R. L. Jilka. Bone marrow, cytokines and bone remodeling. *The New England Journal of Medicine*. 323:305-311, 1995.
231. Marcus, J. N., P. Watson, D. L. Page, and H. T. Lynch. Pathology and heredity of breast cancer in younger women. *Journal of the National Cancer Institute Monographs*:23-33, 1994.
232. Margulies, J. Y., A. Simkin, I. Leichter, et al. Effect of intense physical activity on the bone mineral content in the lower limbs of young adults. *Journal of Bone and Joint Surgery*. 68A:1090-1093, 1986.
233. Mariette, X., C. Bergot, P. Ravaud, et al. Evolution of bone densitometry in patients with myeloma treated with conventional or intensive therapy. *Cancer*. 76:1559-1563, 1995.
234. Mariette, X., P. Khalifa, P. Ravaud, et al. Bone densitometry in patients with multiple myeloma. *American Journal of Medicine*. 93:595-598, 1992.
235. Mars, M., S. Govender, A. Weston, et al. High intensity exercise: A cause of lymphocyte apoptosis? *Biochemical and Biophysical Research Communications*. 249:366-370, 1998.
236. Matkovic, V., K. Kostial, I. Simonovic, et al. Bone status and fracture rates in two regions of Yugoslavia. *American Journal of Clinical Nutrition*. 32:540-549, 1979.

237. Mayer, O. and L. O'Connor. Rehabilitation of persons with cancer - Oncology Nursing Society position statement. *Oncology Nursing Forum*. 16:433, 1989.
238. Mazess, R., B. Collick, J. Trempe, et al. Performance evaluation of a dual-energy X-ray bone densitometer. *Calcified Tissue International*. 44:228-232, 1989.
239. Mazess, R. B. and G. D. Whedon. Immobilisation and bone. *Calcified Tissue International*. 35:605-612, 1983.
240. McCarthy, D. A. and M. M. Dale. The leucocytosis of exercise: A review and model. *Sports Medicine*. 6:333-363, 1988.
241. McCoy-Adabody, A. M. and D. L. Borger. Selected critical care complications of cancer therapy. *AACN Clinical Issues*. 7:26-36, 1996.
242. McGinnis, J. M. The public health burden of a sedentary lifestyle. *Medicine and Science in Sports and Exercise*. 24:S196-S200, 1992.
243. Mellette, S. J. Cancer rehabilitation. *Journal of the National Cancer Institute*. 85:781-784, 1993.
244. Mickel, R. A., D. J. Kessler, J. M. G. Taylor, and A. Lichtenstein. Natural killer cell cytotoxicity in the peripheral blood, cervical lymph nodes and tumor of head and neck cancer patients. *Cancer Research*. 48:5017-5022, 1988.
245. Miller, E. A. Influence of training and inactivity on muscle strength. *Archives of Physical Medicine and Rehabilitation*. 51:499-462, 1970.
246. Mock, V., M. B. Burke, P. Sheehan, et al. A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. *Oncology Nursing Forum*. 21:899-907, 1994.
247. Mock, V., K. Hassey Dow, C. J. Meares, et al. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. *Oncology Nursing Forum*. 24:991-1000, 1997.
248. Moinpour, C. M. Measuring quality of life: An emerging science. *Seminars in Oncology*. 21:48-63, 1994.
249. Molrine, D. C., E. C. Guinan, and J. H. Antin. Haemophilus influenzae type b (HIB)-conjugate immunization before bone marrow harvest in autologous bone marrow transplantation. *Bone Marrow Transplantation*. 17:271-290, 1996.
250. Moolten, D. N. Peripheral blood stem cell transplant: Future directions. *Seminars in Oncology*. 22:271-290, 1995.

## Bibliography

251. Mosan, J., F. Meyer, and S. Gingras. Leisure physical activity and age at menarche. *Medicine and Science in Sports and Exercise*. 23:1170-1175, 1991.
252. Mulligan, K. and A. S. Bloch. Energy expenditure and protein metabolism in human immunodeficiency virus infection and cancer cachexia. *Seminars in Oncology*. 25:82-89, 1998.
253. Muths, E. and O. J. Reichman. Kangaroo rat bone compared to white rat bone after short-term disuse and exercise. *Comparative Biochemical Physiology*. 114A:355-361, 1996.
254. Nash, H. L. Can exercise make us immune to disease? *The Physician and Sportsmedicine*. 14:250-253, 1986.
255. Neal, A. J., K. Evans, and P. J. Hoskin. Does long-term administration of tamoxifen affect bone mineral density. *European Journal of Cancer*. 29A:1971-1973, 1993.
256. Nehlsen-Cannarella, S. L., D. C. Nieman, A. J. Balk-Lamberton, et al. The effects of moderate exercise training on immune response. *Medicine and Science in Sports and Exercise*. 23:64-70, 1991.
257. Nelson, J. P. Perceived health, self-esteem, health habits, and perceived benefits and barriers to exercise in women who have and who have not experienced stage I breast cancer. *Oncology Nursing Forum*. 18:1191-1197, 1991.
258. Nieman, D. Exercise immunology: Practical applications. *International Journal of Sports Medicine*. 18:S91-S100, 1997.
259. Nieman, D. C. Exercise, infection, and immunity. *International Journal of Sports Medicine*. 15:S131-S141, 1994.
260. Nieman, D. C., D. Brendle, D. A. Henson, et al. Immune function in athletes versus nonathletes. *International Journal of Sports Medicine*. 16:329-333, 1995.
261. Nieman, D. C., V. D. Cook, D. A. Henson, et al. Moderate exercise training and natural killer cell cytotoxic activity in breast cancer patients. *International Journal of Sports Medicine*. 16:334-337, 1995.
262. Nieman, D. C., D. A. Henson, G. Gusewitch, et al. Physical activity and immune function in elderly women. *Medicine and Science in Sports and Exercise*. 25:823-831, 1993.
263. Nieman, D. C., A. R. Miller, D. A. Henson, et al. Effect of high- versus moderate-intensity exercise on lymphocyte subpopulations and proliferative response. *International Journal of Sports Medicine*. 15:199-206, 1994.

264. Nieman, D. C., A. R. Miller, D. A. Henson, et al. Effects of high- versus moderate-intensity exercise on natural killer cell activity. *Medicine and Science in Sports and Exercise*. 25:1126-1134, 1993.
265. Nieman, D. C., S. L. Nehlsen-Cannarella, P. A. Markoff, et al. The effects of moderate exercise training on natural killer cells and acute upper respiratory tract infections. *International Journal of Sports Medicine*. 11:467-473, 1990.
266. Nieman, D. C. and S. L. Nehlsen-Cannarella. *The effects of endurance exercise on the immune response*. Oxford: Blackwell Scientific Publications, 1991.
267. Nieman, D. C. and B. K. Pedersen. Exercise and immune function. *Sports Medicine*. 27:73-80, 1999.
268. Nilsson, B. E. C. and N. E. Westlin. Bone density in athletes. *Clinical Orthopaedics*. 77:179-182, 1971.
269. Nordin, M. and V. H. Frankel. *Basic Biomechanics of the Musculoskeletal System*. 2nd ed. Philadelphia: Lea & Febiger, 1989.
270. North, T. C., P. McCullagh, and Z. V. Tran. Effect of exercise on depression. *Exercise and Sport Science Review*. 18:379-415, 1990.
271. Norton, K. and T. Olds. *Anthropometrica: A textbook of body measurement for sports and health courses*. Sydney: University of NSW Press, 1996.
272. Norum, J. and E. Wist. Psychological distress in survivors of Hodgkin's disease. *Support Care Cancer*. 4:191-195, 1996.
273. Novick, W. M., M. Nusbaum, and T. P. Stein. The energy costs of surgery as measured by the doubly labeled water (2H218O) method. *Surgery*. 103:99-106, 1988.
274. Ogilvie, G. K. Interventional Nutrition for the Cancer Patient. *Clinical Techniques in Small Animal Practice*. 13:224-231, 1998.
275. Oliveria, S. A., H. W. Kohl, D. Trichopoulos, and S. N. Blair. The association between cardiorespiratory fitness and prostate cancer. *Medicine and Science in Sports and Exercise*. 28:97-104, 1996.
276. O'Neill, G. Stress, exercise and the human immune system. *Sport Health*. 10:6-7, 1992.
277. O'Shea, J. and J. R. Ortaldo. *The biology of natural killer cells: Insights into the molecular basis of function*. Oxford: IRL Press at Oxford University Press, 1992, 1-40.
278. O'Soba, D. *Measuring the effect of cancer on quality of life*. CRC: Boca Taton, 1991, 25-40.

## Bibliography

279. O'Toole, M. *Encyclopedia & Dictionary of Medicine, Nursing and Allied Health*. 5th ed. Philadelphia: W B Saunders Company, 1992.
280. Paffenbarger, R. S., R. T. Hyde, and A. L. Wing. Physical activity, all-cause mortality and longevity of college alumni. *New England Journal of Medicine*. 341:605-613, 1986.
281. Paffenbarger, R. S., R. T. Hyde, and A. L. Wing. Physical activity and incidence of cancer in diverse populations: A preliminary report. *American Journal of Clinical Nutrition*. 45:312-317, 1987.
282. Parker, A. W. Physical activity and skeletal health in children. In: *Sports and Children*. K. M. Chan and L. J. Micheli (Eds.) Hong Kong: Williams & Wilkie, 1997, pp. 17-38.
283. Pate, R. R. Recent statements and initiatives on physical activity and health. *Quest*. 47:304-310, 1995.
284. Peat, I. D., S. Healy, D. M. Reid, and S. H. Ralston. Steroid induced osteoporosis: An opportunity for prevention? *Annals of the Rheumatic Diseases*. 54:66-68, 1995.
285. Pedersen, B. J., A. Schlemmer, C. Hassager, and C. Christiansen. Changes in the carboxyl-terminal propeptide of type I procollagen and other markers of bone formation upon five days of bed rest. *Bone*. 17:91-95, 1995.
286. Pedersen, B. K. Influence of physical activity on the cellular immune system: Mechanisms of action. *International Journal of Sports Medicine*. 12:S23-S29, 1991.
287. Pedersen, B. K. and H. Bruunsgaard. How physical exercise influences the establishment of infections. *Sports Medicine*. 19:393-400, 1995.
288. Pedersen, B. K., N. Tvede, and L. D. Christensen. Natural killer cell activity in peripheral blood of highly trained and untrained persons. *International Journal of Sports Medicine*. 10:129-131, 1989.
289. Pedersen, B. K. and H. Ullum. NK cell response to physical activity: Possible mechanisms of action. *Medicine and Science in Sports and Exercise*. 26:140-146, 1994.
290. Pender, N. J. *Health promotion in nursing practice*. Norwalk: Appleton & Lange, 1987.
291. Peters, C., H. Lotzerich, H. G. Hoff, et al. Influence of endurance training on the natural cytotoxicity in cancer patients. In *Proceedings of German Sports Medicine Congress*. Paderborn: University of Paderborn, 1993.

292. Peters, C., H. Lotzerich, B. Niemeier, et al. Influence of a moderate exercise training on natural killer cytotoxicity and personality traits in cancer patients. *Anticancer Research*. 14:1033-1036, 1994.
293. Peters, C., H. Lotzerich, B. Niemeir, et al. Exercise, cancer and the immune response of monocytes. *Anticancer Research*. 15:175-180, 1995.
294. Pinto, B. M. and B. H. Marcus. Physical activity, exercise and cancer in women. *Medicine, Exercise, Nutrition and Health*. 3:102-111, 1994.
295. Pinto, B. M. and N. C. Maruyama. Exercise in the rehabilitation of breast cancer survivors. *Psycho-Oncology*. 8:191-206, 1999.
296. Piovesan, A., A. Berruti, M. Torta, et al. Comparison of assay of total and bone-specific alkaline phosphatase in the assessment of osteoblast activity in patients with metastatic bone disease. *Calcified Tissue International*. 61:362-369, 1997.
297. Ploutz-Snyder, L. L., P. A. Tesch, B. M. Hather, and G. A. Dudley. Vulnerability to dysfunction and muscle injury after unloading. *Archives of Physical Medicine and Rehabilitation*. 77:773-777, 1996.
298. Pocock, N. A., J. A. Eisman, M. G. Yeates, et al. Physical fitness is a major determinant of femoral neck and lumbar spine bone mineral density. *Journal of Clinical Investigations*. 78:618-321, 1986.
299. Polednak, A. P. College athletics, body size and cancer mortality. *Cancer*. 38:382-387, 1976.
300. Pollock, M. and J. Wilmore. *Exercise in health and disease*. 2nd ed. Philadelphia: W. B. Saunders, 1990.
301. Pollock, M. L., D. H. Schmidt, and A. S. Jackson. Measurement of cardiorespiratory fitness and body composition in the clinical setting. *Comprehensive Therapy*. 6:12-27, 1980.
302. Potempa, K., L. T. Braun, T. Tinknell, and J. Popovich. Benefits of aerobic exercise after stroke. *Sports Medicine*. 21:337-346, 1996.
303. Potera, C. Exercise and breast cancer risk. *News Brief*. 23:37-38, 1995.
304. Powell, K. E. and S. N. Blair. The public health burdens of sedentary living habits: theoretical but realistic estimates. *Medicine and Science in Sports and Exercise*. 26:851-856, 1994.
305. Powers, S. K. and E. T. Howley. *Exercise Physiology: Theory and Application to Fitness and Performance*. 2nd ed. Wisconsin: WCB Brown & Benchmark Publishers, 1994.

## Bibliography

306. Powles, T. J., T. Hickidi, and J. A. Kanis. Effect of tamoxifen on bone mineral density measured by dual energy X-ray absorptiometry in healthy premenopausal and postmenopausal women. *Journal of Clinical Oncology*. 14:78-84, 1996.
307. Pross, H. F. and E. Lotzova. Role of natural killer cells in cancer - a review. *Natural Immunity*. 12:279-292, 1993.
308. Pyne, D. B. Regulation of neutrophil function during exercise. *Sports Medicine*. 17:245-258, 1994.
309. Pyne, D. B., M. S. Baker, P. A. Fricker, et al. Effects of an intensive 12-wk training program by elite swimmers on neutrophil oxidative activity. *Medicine and Science in Sports and Exercise*. 27:536-542, 1995.
310. Queensland Medical Laboratories. Trace - Alkaline Phosphatase Reagent, 1999.
311. Radetti, G., C. Castellan, L. Tato, et al. Bone mineral density in children and adolescent females treated with high doses of L-Thyroxine. *Hormone Research*. 39:127-131, 1993.
312. Rambaut, P. C. and A. W. Goode. Skeletal changes during space flight. *Lancet*. 2:1050-1052, 1985.
313. Ravussin, E., I. T. Harper, R. Rising, and C. Bogardus. Energy expenditure by doubly labeled water: validation in lean and obese subjects. *American Journal of Physiology*. 261:E402-E409, 1991.
314. Ravussin, E., S. Lillioja, T. E. Anderson, et al. Determinants of 24 hour energy expenditure in man: methods and results using a respiration chamber. *Journal of Clinical Investigations*. 78:1568-1578, 1986.
315. Ream, E. and A. Richardson. From theory to practice: Designing interventions to reduce fatigue in patients with cancer. *Oncology Nursing Forum*. 26:1295-1303, 1999.
316. Reilly, J. J. and P. Workmen. Is body composition an important variable in the pharmacokinetics of anticancer drugs? *Cancer Chemotherapy and Pharmacology*. 34:3-13, 1994.
317. Rhind, S. G., P. N. Shek, S. Shinkai, and R. J. Shephard. Differential expression of interleukin-2 receptor alpha and beta chains in relation to natural killer cell subsets and aerobic fitness. *International Journal of Sports Medicine*. 15:911-918, 1994.
318. Richardson, A. Fatigue in cancer patients: A review of the literature. *European Journal of Cancer Care*. 4:20-32, 1995.

319. Rigsby, L., P. Raven, R. Dishman, and A. Jackson. The effects of exercise on HIV+ individuals. *Medicine and Science in Sports and Exercise*. 51:S109 (Abstract), 1989.
320. Rigsby, L. W., R. K. Dishman, A. W. Jackson, et al. Effects of exercise training on men seropositive for the human immunodeficiency virus-1. *Medicine and Science in Sport and Exercise*. 24:6-12, 1992.
321. Riis, B. J. Biochemical markers of bone turnover in diagnosis and assessment of therapy. *The American Journal of Medicine*. 91:S64-S68, 1991.
322. Ringdal, G. I., K. Ringdal, S. Kvinnsland, and S. G. Gotestam. Quality of life of cancer patients with different prognoses. *Quality of Life Research*. 3:143-154, 1994.
323. Romeyn, M. and N. Gunn. Resistance exercise and oxandrolone for men with HIV-related weight loss. *Journal of the American Medical Association*. 284:176, 2000.
324. Rook, A. An investigation into the longevity of Cambridge sportsmen. *British Medical Journal*. 1:773-777, 1954.
325. Rosenberg, R. Health-related quality of life between naturalism and hermeneutics. *Social Science and Medicine*. 41:1411-1415, 1995.
326. Rosenstein, A. H. The benefits of health maintenance. *The Physician and Sportsmedicine*. 15:57-68, 1987.
327. Roubenoff, R., R. A. Roubenoff, J. G. Cannon, et al. Rheumatoid cachexia: Cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. *The Journal of Clinical Investigations*. 93:2379-2386, 1994.
328. Rougier, P. Introduction - colorectal cancer. *European Journal of Cancer*. 32A:S1, 1996.
329. Ryan, A. S., M. S. Treuth, G. R. Hunter, and D. Elahi. Resistive training maintains bone mineral density in postmenopausal women. *Calcified Tissue International*. 62:295-299, 1998.
330. Ryan, A. S., M. S. Treuth, M. A. Rubin, et al. Effects of strength training on bone mineral density: hormonal and bone turnover relationships. *Journal of Applied Physiology*. 77:1678-1684, 1994.
331. Sakurai, Y. and S. Klein. Metabolic alteration in patients with cancer: Nutritional implications. *Surgery Today*. 28:247-257, 1998.
332. Sandler, R. B., C. W. Slemenda, R. E. La Porte, et al. Postmenopausal bone density and milk consumption in childhood and adolescence. *American Journal of Clinical Nutrition*. 42:270-274, 1985.

## Bibliography

333. Schag, C. A. C., P. A. Ganz, D. S. Wing, et al. Quality of life in adult survivors of lung, colon and prostate cancer. *Quality of Life Research*. 3:127-141, 1994.
334. Schag, C. A. C. and R. L. Heinrich. Development of a comprehensive quality of life measurement tool: CARES. *Oncology*. 4:135-147, 1990.
335. Schag, C. C., R. L. Heinrich, R. L. Aadland, and P. A. Ganz. Assessing problems of cancer patients: psychometric properties of the Cancer Inventory of Problem Situations. *Health Psychology*. 9:83-102, 1990.
336. Schag, C. C., R. L. Heinrich, and P. A. Ganz. The Cancer Inventory of Problem Situations: An instrument for assessing cancer patients' rehabilitation needs. *Journal of Psychosocial Oncology*. 1:11-24, 1983.
337. Scheid, C., R. Pettengell, M. Ghielmini, et al. Time-course of the recovery of cellular immune function after high-dose chemotherapy and peripheral blood progenitor cell transplantation for high-grade non-Hodgkin's lymphoma. *Bone Marrow Transplantation*. 15:901-906, 1995.
338. Schell, J. and B. Leelarthapin. *Physical Fitness Assessment in Exercise and Sport Science*. New South Wales: Biomediscience Services, 1994.
339. Schmid, L. *Malignant tumours as causes of death of former athletes*. Basel: Birkhauser Verlag, 1975, 85-91.
340. Schoeller, D. A. and C. R. Fjeld. Human energy metabolism: What have we learned from the doubly labeled water method? *Annual Reviews of Nutrition*. 11:355-373, 1991.
341. Schoeller, D. A., E. Ravussin, Y. Schutz, et al. Energy expenditure by doubly labeled water: Validation in humans and proposed calculation. *American Journal of Physiology*. 250:R823-R830, 1986.
342. Schwartz, A. L. Daily fatigue patterns and effect of exercise in women with breast cancer. *Cancer Practice*. 8:16-24, 2000.
343. Schwartz, A. L. Fatigue mediates the effects of exercise on quality of life. *Quality of Life Research*. 8:529-538, 1999.
344. Schwatz, A. L. Patterns of exercise and fatigue in physically active cancer survivors. *Oncology Nursing Forum*. 25:485-491, 1998.
345. Seibel, M. J., F. Gartenberg, S. J. Silverberg, et al. Urinary hydroxypyridium cross-links of collagen in primary hyperparathyroidism. *Journal of Clinical Endocrinology Metabolism*. 74:481-486, 1992.
346. Shephard, R. J. *Body Composition in Biological Anthropology*. London: Cambridge University Press, 1989.

347. Shephard, R. J. Does exercise reduce all-cancer death rates? *British Journal of Sports Medicine*. 26:125-128, 1992.
348. Shephard, R. J. Exercise and malignancy. *Sports Medicine*. 3:235-241, 1986.
349. Shephard, R. J. Exercise, immune function and HIV infection. *Journal of Sports Medicine and Physical Fitness*. 38:101-110, 1998.
350. Shephard, R. J. Exercise in the prevention and treatment of cancer: An update. *Sports Medicine*. 15:258-280, 1993.
351. Shephard, R. J. Physical activity and reduction of health risks: How far are the benefits independent of fat loss? *The Journal of Sports Medicine and Physical Fitness*. 34:91-98, 1994.
352. Shephard, R. J., S. Rhind, and P. N. Shek. Exercise and the immune system: Natural killer cells, interleukins and related responses. *Sports Medicine*. 18:340-369, 1994.
353. Shephard, R. J. and P. N. Shek. Cancer, immune function, and physical activity. *Canadian Journal of Applied Physiology*. 20:1-25, 1995.
354. Shephard, R. J. and P. N. Shek. Potential impact of physical activity and sport on the immune system - a brief review. *British Journal of Sports Medicine*. 28:247-255, 1994.
355. Shephard, R. J., T. J. Verde, S. G. Thomas, and P. Shek. Physical activity and the immune system. *Canadian Journal of Sports Science*. 16:163-185, 1991.
356. Shevde, L. A., N. N. Joshi, S. B. Dudhat, et al. Immune functions, clinical parameters and hormone receptor status in breast cancer patients. *Journal of Cancer Research and Clinical Oncology*. 125:313-320, 1999.
357. Shike, M., R. D. McRusell, and A. S. Detsky. Changes in body composition in patients with small-cell lung cancer. *Annals of Internal Medicine*. 101:303, 1984.
358. Shinkai, S., H. Kohno, K. Kimura, et al. Physical activity and immune senescence in men. *Medicine and Science in Sports and Exercise*. 27:1516-1526, 1995.
359. Shore, S. and R. J. Shephard. Immune responses to exercise in children treated for cancer. *The Journal of Sports Medicine and Physical Fitness*. 39:240-243, 1999.
360. Sibbitt, W. L., A. D. Bankhurst, A. J. Jumonville, et al. Defects in natural killer cell activity and interferon response in human lung carcinoma and malignant melanoma. *Cancer Research*. 44:852-856, 1984.

## Bibliography

361. Simon, H. B. Exercise and infection. *Physician and Sportsmedicine*. 15:134-141, 1987.
362. Simons, J. P. F. H. A., A. M. W. J. Schols, J. M. J. Hoefnagels, et al. Effects of medroxyprogesterone acetate on food intake, body composition, and resting energy expenditure in patients with advanced, nonhormone-sensitive cancer. *Cancer*. 82:553-560, 1998.
363. Simons, J. P. F. H. A., A. M. W. J. Schols, K. R. Westerterp, et al. Bioelectrical impedance analysis to assess changes in total body water in patients with cancer. *Clinical Nutrition*. 18:35-39, 1999.
364. Simons, J. P. F. H. A., A. M. W. J. Schols, K. R. Westerterp, et al. The use of bioelectrical impedance analysis to predict total body water in patients with cancer cachexia. *American Journal of Clinical Nutrition*. 61:741-745, 1995.
365. Skerry, T. M. and L. E. Lanyon. Interruption of disuse by short duration walking exercise does not prevent bone loss in the sheep calcaneus. *Bone*. 16:269-274, 1995.
366. Slemenda, C. W., J. Z. Miller, S. L. Hui, et al. Role of physical activity in the development of skeletal mass in children. *Journal of Bone and Mineral Research*. 6:1227-1233, 1991.
367. Smets, E. M., B. Garssen, A. L. J. Schuster-Uitterhoeve, and J. C. J. M. de Haes. Fatigue in cancer patients. *British Journal of Cancer*. 68:2204, 1993.
368. Smith, J. A. Guidelines, standards, and perspectives in exercise immunology. *Medicine and Science in Sports and Exercise*. 27:497-506, 1995.
369. Smith, S. L. Physical exercise as an oncology nursing intervention to enhance quality of life. *Oncology Nursing Forum*. 23:771-778, 1996.
370. Spence, D. W., M. A. Galantino, K. A. Mossberg, and S. O. Zimmerman. Progressive resistance exercise: Effect on muscle function and anthropometry of a select AIDS population. *Archives of Physical Medicine and Rehabilitation*. 71:644-648, 1990.
371. Spitzer, G., D. R. Adkins, V. Spencer, et al. Randomized study of growth factors post-peripheral blood stem-cell transplant: Neutrophil recovery is improved with modest clinical benefits. *Journal of Clinical Oncology*. 12:661-670, 1994.
372. Staal-van den Brekel, A. J., A. M. W. J. Schols, G. P. M. ten Velde, et al. Analysis of the energy balance in lung cancer patients. *Cancer Research*. 54:6430-6433, 1994.
373. Stedman, T. Approaches to measuring quality of life and their relevance to mental health. *Australian and New Zealand Journal of Psychiatry*. 30:731-740, 1996.

374. Steinhauer, E. H., A. T. Doyle, J. Reed, and A. S. Kadish. Defective natural cytotoxicity in patients with cancer: normal number of effector cells but increased recycling capacity in patients with advanced disease. *Journal of Immunology*. 5:2255-2259, 1982.
375. Stern, J. M., Chesnut. H. C., B. Bruemmer, K. M. Sullivan, et al. Bone density loss during treatment of chronic GVHD. *Bone Marrow Transplantation*. 17:395-400, 1996.
376. Sternfeld, B. Cancer and the protective effect of physical activity: The epidemiology evidence. *Medicine and Science in Sports and Exercise*. 24:1195-1209, 1992.
377. Stoll, B. A. Diet and exercise regimens to improve breast carcinoma prognosis. *Cancer*. 78:2465-2470, 1996.
378. Stracke, H. and W. Kuhnel. *Biochemical Parameters in the Diagnosis of Bone Diseases*. San Francisco: Polyglot Language Service.
379. Strang, P. The effect of megestrol acetate on anorexia, weight loss and cachexia in cancer and AIDS patients (review). *Anticancer Research*. 17:657-662, 1997.
380. Stubbs, D. Skeletal function and weightlessness: A mechanism for hypogravic skeletal atrophy. *Aerospace Medicine*:1126-1128, 1970.
381. Sukkar, S. G., A. Giacosa, and F. Frascio. Clinical validation of bioelectrical impedance (BIA) in malnourished cancer patients. *RINPE*. 11:78, 1993.
382. Sulzman, F. M. Life sciences space missions - Overview. *Journal of Applied Physiology*. 81:3-6, 1996.
383. Svedlund, J., M. Sullivan, I. Sjodin, et al. Quality of life in gastric cancer patients prior to gastrectomy. *Quality of Life Research*. 5:255-264, 1996.
384. Talmadge, J. E., E. Reed, K. Ino, et al. Rapid immunologic reconstitution following transplantation with mobilized peripheral blood stem cells as compared to bone marrow. *Bone Marrow Transplantation*. 19:161-172, 1997.
385. Taskinen, M. and U. M. Saarinen. Skeletal muscle protein reserve after bone marrow transplantation in children. *Bone Marrow Transplantation*. 18:937-941, 1996.
386. Tavani, A., C. Braga, C. La Vecchia, et al. Attributable risks for breast cancer in Italy: Education, family history and reproductive and hormonal factors. *International Journal of Cancer*. 70:159-163, 1997.

## Bibliography

387. Thomas, T., L. Vico, T. M. Skerry, et al. Architectural modifications and cellular response during disuse-related bone loss in calcaneus of the sheep. *American Journal of Physiology*. 80:198-202, 1996.
388. Thune, I. Physical exercise in rehabilitation programs for cancer patients? *Journal of Alternative and Complementary Medicine*. 4:205-207, 1998.
389. Tilton, F. E., J. J. C. Degianni, and V. S. Schneider. Long-term follow-up of Skylab bone demineralisation. *Aviation, Space and Environmental Medicine*. 51:1209-1213, 1980.
390. Tisdale, M. J. Cancer Cachexia: Metabolic alterations and clinical manifestations. *Nutrition*. 13:1-7, 1997.
391. Tsutsi, S., M. Moirta, H. Kuwano, et al. Influence of preoperative treatment and surgical operation on immune function of patients with oesophageal carcinoma. *Journal of Surgical Oncology*. 49:176-181, 1992.
392. Tvede, N., M. Kappel, J. Halkjaer-Kristensen, et al. The effect of light, moderate and severe bicycle exercise on lymphocyte subsets, natural and lymphokine activated killer cells, lymphocyte proliferative response and interleukin 2 production. *International Journal of Sports Medicine*. 14:275-282, 1993.
393. Uh, S., S. M. Lee, H. T. Kim, et al. The effect of radiation therapy on immune function in patients with squamous cell lung carcinoma. *Chest*. 105:132-137, 1994.
394. Uhlenbruck, G. and U. Order. Can endurance sports stimulate immune mechanisms against cancer and metastasis? *International Journal of Sports Medicine*. 12:S63-S68, 1991.
395. Uthoff, H. K. and Z. F. Jaworski. Bone loss in response to long-term immobilisation. *Journal of Bone and Joint Surgery*. 60B:420-429, 1978.
396. Ullum, H., J. Palmo, J. Halkjaer-Kristensen, et al. The effect of acute exercise on lymphocyte subsets, natural killer cells, proliferative responses, and cytokines in HIV-seropositive persons. *Journal of Acquired Immune Deficiency Syndromes*. 7:1122-1133, 1994.
397. Uyl de Groot, C. A., P. C. Huijgens, and F. F. H. Rutten. Colony-stimulating factors and peripheral blood progenitor cell transplantation. *PharmacoEconomics*. 10:23-35, 1996.
398. Valimaki, M. J., K. Kinnunen, L. Volin, et al. A prospective study of bone loss and turnover after allogenic bone marrow transplantation: Effect of calcium supplementation with or without calcitonin. *Bone Marrow Transplantation*. 23:355-361, 1999.

399. van der Wiel, H. P., P. Lips, J. Nauta, et al. Intranasal calcitonin suppresses increased bone resorption during short-term immobilization: A double blind study of the effects of intranasal calcitonin on biochemical parameters of bone turnover. *Journal of Bone and Mineral Research*. 8:1459-1465, 1993.
400. van Schayck, C. P. Measurement of quality of life in patients with chronic obstructive pulmonary disease. *PharmacoEconomics*. 11:13-18, 1997.
401. Varricchio, M., A. Gambardella, V. Balbi, et al. The oncological therapy in the elderly. *Archives of Gerontology, Geriatrics*. Suppl 5:593-598, 1996.
402. Vassilopoulou-Sellin, R., P. Brosnan, A. Delpassand, et al. Osteopenia in young survivors of childhood cancer. *Medical and Pediatric Oncology*. 32:272-278, 1999.
403. Verloop, J., M. A. Rookus, K. van der Kooy, and F. E. van Leeuwen. Physical activity and breast cancer risk in women aged 20-54 years. *Journal of the National Cancer Institute*. 92:128-135, 2000.
404. Verrill, D. E. and P. M. Ribisl. Resistive exercise training in cardiac rehabilitation. *Sports Medicine*. 21:347-383, 1996.
405. Villaneuva, R. Rehabilitation needs of cancer patients. *Southern Medical Journal*. 68:169-172, 1975.
406. Visser, M. C., P. J. Koudstaal, R. A. M. Erdman, et al. Measuring quality of life in patients with myocardial infarction or stroke: A feasibility study of four questionnaires in The Netherlands. *Journal of Epidemiology and Community Health*. 49:513-517, 1995.
407. Wahlqvist, M. L. and A. Kouris-Blazos. *Dietary advice and food guidance systems*. St Leonards, New South Wales: Allen & Unwin Pty Ltd, 1997.
408. Wahner, H. W., W. L. Dunn, R. B. Mazess, et al. Dual photon (Gd-153) absorptiometry of bone. *Radiology*. 156:203-206, 1985.
409. Wardlaw, G. M. and A. M. Pike. The effect of lactation on peak adult shaft and ultra-distal forearm bone mass in women. *American Journal of Clinical Nutrition*. 44:283-286, 1986.
410. Warner, J. T., W. Bell, D. K. H. Webb, and J. W. Gregory. Daily energy expenditure and physical activity in survivors of childhood malignancy. *Pediatric Research*. 43:607-613, 1998.
411. Warner, J. T., W. Bell, D. K. H. Webb, and J. W. Gregory. Relationship between cardiopulmonary response to exercise and adiposity in survivors of childhood malignancy. *Archives of Disease in Childhood*. 76:298-303, 1997.

## Bibliography

412. Warner, J. T., W. D. Evans, D. K. H. Webb, et al. Relative osteopenia after treatment for acute lymphoblastic leukaemia. *Pediatric Research*. 45:544-551, 1999.
413. Watchie, J. Cardiopulmonary complications of cancer treatment. *Clinical Management*. 12:92-95, 1992.
414. Watson, P. G. Cancer rehabilitation: The evolution of a concept. *Cancer Nursing*. 13:2-12, 1990.
415. Watson, P. G. The optimal functioning plan. *Cancer Nursing*. 15:254-263, 1992.
416. Weicker, H. and E. Werle. Interaction between hormones and the immune system. *International Journal of Sports Medicine*. 12:S30-S37, 1991.
417. Weidemann, M. J., J. A. Smith, A. B. Gray, et al. Exercise and the immune system. *Today's Life Science*. July:24-33, 1992.
418. Weir, J. D. New methods for calculating metabolic rate with special reference to protein metabolism. *Journal of Physiology*. 109:1-9, 1949.
419. Welch, R. D., R. B. Ashman, K. J. Baker, and R. H. Browne. Intraosseous infusion of prostaglandin E2 prevents disuse-induced bone loss in the tibia. *Journal of Orthopaedic Research*. 14:3030, 1996.
420. Weston, P. M. T., R. F. King, A. W. Goode, and N. S. Williams. Diet induced thermogenesis in patients with gastrointestinal cancer cachexia. *Clinical Science*. 79:133-138, 1989.
421. Williams, J. A., J. Wagner, R. Wasnich, and L. Heilbrum. The effect of long-distance running upon appendicular bone mineral content. *Medicine and Science in Sports and Exercise*. 16:223-227, 1984.
422. Wilmore, J. H. and D. L. Costill. *Physiology of Sport and Exercise*. Champaign: Human Kinetics, 1994.
423. Wiltscheke, C. H., M. Krainer, A. C. Budinsky, A. Berger, et al. Reduced mitogenic stimulation of peripheral blood mononuclear cells as a prognostic parameter for the course of breast cancer: A prospective longitudinal study. *British Journal of Cancer*. 71:1292-1296, 1995.
424. Wingard, J. R., B. Curbow, F. Baker, and L. Piantadosi. Health, functional status and employment of adult survivors of bone marrow transplantation. *Annals of Internal Medicine*. 114:113-118, 1991.
425. Winningham, M. L. *Exercise and Cancer*. Philadelphia: F A Darr, 1994.
426. Winningham, M. L. Walking program for people with cancer. *Cancer Nursing*. 14:270-276, 1991.

427. Winningham, M. L. and M. G. MacVicar. The effect of aerobic exercise on patients' reports of nausea. *Oncology Nursing Forum*. 15:447-450, 1988.
428. Winningham, M. L., M. G. MacVicar, M. Bondoc, et al. Effect of aerobic exercise on body weight and composition in patients with breast cancer on adjuvant chemotherapy. *Oncology Nursing Forum*. 16:683-689, 1989.
429. Winningham, M. L., M. G. MacVicar, and C. A. Burke. Exercise for cancer patients: Guidelines and precautions. *The Physician and Sportsmedicine*. 14:125-134, 1986.
430. Winningham, M. L., L. M. Nail, M. B. Burke, et al. Fatigue and the cancer experience: The state of the knowledge. *Oncology Nursing Forum*. 21:23-36, 1994.
431. Withold, W., S. Gegenhardt, M. Heins, et al. Monitoring of bone resorption after renal transplantation by measuring the urinary excretion of pyridinium cross-links. *European Journal of Clinical Chemistry and Clinical Biochemistry*. 33:15-21, 1995.
432. Withold, W., H. Khakzad, G. Georgescu, et al. Efficacy of simultaneous determination of bone alkaline phosphatase mass concentrations in serum and urinary excretion of pyridinium cross-links for detection of bone metastases. *Clinical Biochemistry*. 28:479-485, 1995.
433. Withold, W., H-H. Wolf, S. Kollbach, et al. Relationship between bone metabolism and plasma cytokine levels in patients at risk of post-transplantation bone disease after bone marrow transplantation. *European Journal of Clinical Chemistry and Clinical Biochemistry*. 34:295-299, 1996.
434. Witten, A., S. Briscoe, and Queensland Medical Laboratories. *Biochemistry Manual - Hydroxyproline*, 2000.
435. Wolf, L. D., L. N. Matheson, D. D. Ford, and A. L. Kwak. Relationships among grip strength, work capacity and recovery. *Journal of Occupational Rehabilitation*. 6:57-70, 1996.
436. Woods, J. A. and J. M. Davis. Exercise, monocyte/macrophage function, and cancer. *Medicine and Science in Sports and Exercise*. 26:147-157, 1994.
437. Woods, J. A., J. M. Davis, M. L. Kohut, et al. Effects of exercise on the immune response to cancer. *Medicine and Science in Sports and Exercise*. 26:1109-1115, 1994.
438. Woods, J. A., J. M. Davis, E. P. Mayer, et al. Exercise increases inflammatory macrophage antitumor cytotoxicity. *Journal of Applied Physiology*. 75:879-886, 1993.

## Bibliography

439. Woods, J. A., J. M. Davis, J. A. Smith, and D. C. Nieman. Exercise and cellular innate immune function. *Medicine and Science in Sports and Exercise*. 31:57-66, 1999.
440. Wright, M. J., J. M. Halton, R. F. Martin, and R. D. Barr. Long-term gross motor performance following treatment for acute lymphoblastic leukaemia. *Medical and Pediatric Oncology*. 31:86-90, 1998.
441. Wronski, T. J. and E. R. Morey. Inhibition of cortical and trabecular bone formation in the long bones of immobilized monkeys. *Clinical Orthopaedics*. 181:269-276, 1983.
442. Yagodovsky, V. S., L. A. Triftanidi, and G. P. Gorokhova. Space flight effects on skeletal bones of rats (light electron microscopic examination). *Aviation, Space and Environmental Medicine*:734-738, 1976.
443. Yamaue, H., H. Tanimura, Y. Aoki, et al. Clinical and immunological evaluation of intraoperative radiation therapy for patients with unresectable pancreatic cancer. *Journal of Surgical Oncology*. 49:10-15, 1992.
444. Yoshioka, H. Rehabilitation for the terminal cancer patient. *American Journal of Physical Medicine Rehabilitation*. 73:199-206, 1994.
445. Young-McCaughan, S. and D. L. Sexton. A retrospective investigation of the relationship between aerobic exercise and quality of life in women with breast cancer. *Oncology Nursing Forum*. 18:751-757, 1991.
446. Young-Moo, N., K. Min-Young, K. Yong-Kyun, et al. Exercise therapy effect on natural killer cell cytotoxic activity in stomach cancer patients after curative surgery. *Archives of Physical Medicine and Rehabilitation*. 81:777-779, 2000.
447. Zahm, S. H., L. Hoffman-Goetz, M. Dosemeci, et al. Occupational physical activity and non-Hodgkin's lymphoma. *Medicine and Science in Sports and Exercise*. 31:566-571, 1999.
448. Zanker, K. S. and R. Kroczeck. Looking along the track of the psychoneuroimmunologic axis for missing links in cancer progression. *International Journal of Sports Medicine*. 12:S58-S62, 1991.