**Review Article**

# Biological markers as an outcome measure of exercise in cancer rehabilitation: A systematic review

## ABSTRACT

The number of people living with and beyond cancer is at an all time high. These survivors are not necessarily living well, as adverse side effects from cancer and its treatment can last up to 5 years and leave patients at a higher risk of developing secondary cancers and other chronic illnesses. Exercise has been proven to be a safe and effective method of intervention to decrease mortality and overall improve health outcomes. The biological mechanism through which this occurs is an area of research that is in its infancy and not well defined. A systematic search was conducted of four databases for relevant randomized controlled trials (RCTs) published between January 2004 and December 2014. Studies had to include any blood/urine biological markers as an outcome measure to a physical activity intervention for cancer survivors posttreatment. Fifteen relevant articles were identified (12 RCTs). It was shown that randomized controlled trials of exercise for cancer survivors posttreatment may results in changes to circulating levels of insulin, insulin related pathways (insulin like growth factor II [IGF II], IGF binding protein 3), high density lipoprotein, total cholesterol, leptin, and osteocalcin. Due to small sample sizes, the evidence is still preliminary and therefore more research is warranted in this area in the form of larger, statistically powered RCTs for cancer survivors.

KEY WORDS: Biomarkers, cancer rehabilitation, cancer survivorship, exercise, physical activity

Lauri-Anne McDermott, Marie H. Murphy[1], Andrea M. McNeilly[1], Jane P. Rankin[2], Jackie H. Gracey

Centre for Health and Rehabilitation Technologies, Institute of Nursing and Health Research, Ulster University, [1]Sport and Exercise Science Research Institute, Ulster University, [3]Department of Physiotherapy, Cancer Centre, Belfast City Hospital, Belfast Health and Social Care Trust, Belfast, Northern Ireland

**For correspondence:**
Dr. Jackie H. Gracey, Room 01F117, School of Health Sciences, Ulster University, Jordanstown Campus, Shore Road, Newtownabbey, Co. Antrim, BT37 0QB, Northern Ireland.
E-mail: jh.gracey@ulster.ac.uk

## INTRODUCTION

Now more than ever, people are living with and beyond their cancer diagnosis. The number of people in the UK surviving more than 5 years from initial diagnosis is predicted to more than double between 2010 and 2030 to 2.7 million.[1] There is therefore a need to develop appropriate person-centered rehabilitation services to improve both the physical and mental health of survivors.

Regular physical activity is associated with lower risk of all-cause mortality and has recently even been stated to be potentially as effective as many drug interventions.[2] Although no formal physical activity guidelines for cancer survivors have been published in the UK, it is widely accepted that cancer survivors should aim to achieve the health-related physical activity guidelines for the general population;[3] however, the feasibility of this is questionable. These guidelines from the Department of Health,[4] include for adults, doing at least 150 minutes of moderate intensity activity a week. This accords with the American College of Sports Medicine (ACSM) recommendations, who state that amount of exercise in cancer survivors is both safe and beneficial for health outcomes.[5]

Exercise interventions and increased physical activity have been well documented in their ability to improve multiple aspects of health in cancer survivors; including quality of life, fatigue, as well as all-cause and cancer-specific mortality. However, the beneficial effects may also manifest themselves in the form of alterations in blood biomarkers known to be associated with cancer or other health-related biochemical mechanisms.[6] The use of such biomarkers can help determine the specific physiology and mechanisms underlying the benefits that exercise elicits on recurrence or progression of cancer.[7] This information can provide a measurable indicator of the progression

Cite this article as: ???

of a participant throughout an exercise intervention and enable better individualization and precise prescription of personalized programs in order to maximize results for the individual.

This review aims to systematically examine the data from this unique and fast growing area of research. By assessing and collating RCTs of the highest quality, the findings from multiple studies were analysed in order to identify any patterns or relationships between the biomarkers used and the results.

## METHODOLOGY

### Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines[8] were followed to identify, screen and report the studies used [Figure 1]. Four electronic databases were searched with a cut-off date of December 9, 2014; Ovid MEDLINE, EMBASE, Scopus, and Cumulative Index to Nursing and Allied Health Plus. The search included human studies on all-type cancers with any blood/salivary/urine biomarkers as an outcome measure.

The key search terms included: Exercise/OR Resistance/OR Training/OR Walking/OR Exercise Therapy/OR Exercise Movement Techniques/OR aerobic training.mp. OR exercise.mp. OR resistance training.mp. OR walking.mp. OR pilates.mp. AND exp Neoplasms/OR cancer.mp. AND exp Biological Markers/OR biomarker*.mp. OR biological marker*.mp. AND posttreatment. mp. OR Survivors/OR survivor*.mp.
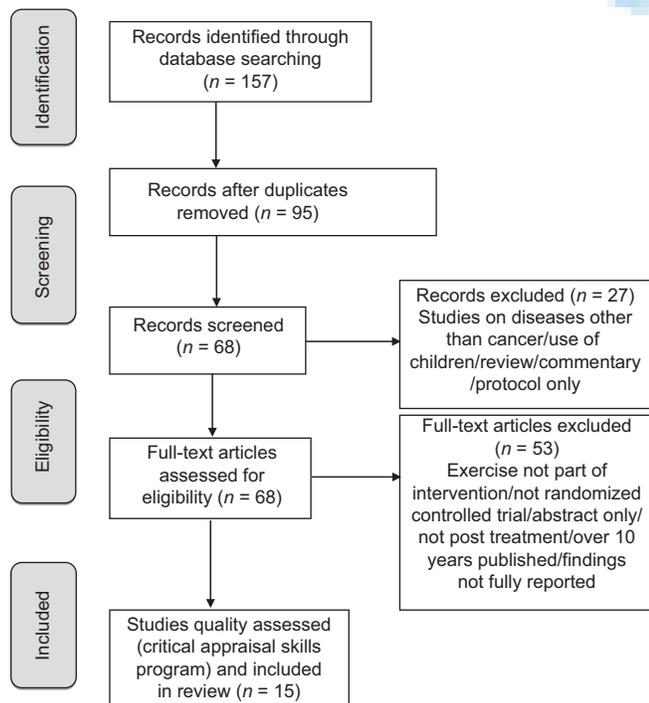


**Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses study flow diagram

Only studies that were available in full-text were included and any that were not readily available online were retrieved from the university library. This search strategy was conducted on two separate occasions; first, one of the authors (L.McD) ran each individual database and recorded the number and name of each title found. Then, the same search was run independently by a university librarian and compared in order to ensure all relevant studies were identified.

### Screening

The titles and abstracts from each database were screened by two of the authors (L.McD and M.M) to determine the eligibility. Studies were considered eligible if they were randomized controlled trials; published between 2004 and 2014; included human participants over the age of 18 years; involved any form of exercise or physical activity intervention of any frequency intensity type or duration (interventions which incorporated supplementary elements such as diet or psychosocial therapy were also included); and reported pre/postmeasurements of at least one blood/salivary/urinary biomarker. Participants with any form of cancer diagnosis and any anticancer treatment administered for curative intent were included but importantly, they needed to be posttreatment (with the exception of those receiving long-term hormone therapy).

Therefore, nonrandomized controlled trials, animal studies or those involving human participants still undergoing cancer treatment or under the age of 18 years were excluded from the review. Exercise interventions in noncancer populations or where biomarkers were not reported as a primary or secondary outcome measure were also excluded.

Once both authors had screened all abstracts, the included studies were then read in full-text by one of the authors (L.McD) to further exclude any ineligible studies. Quality assessment was completed using the Critical Appraisal Skills Program (CASP)[9] tool. Two of the authors (L.McD and A.McN) independently completed the 11 question checklist for each study and then results were compared.

## RESULTS

The search identified 157 articles, which was reduced to 95 after duplicates were removed [Figure 1]. A total of 80 out of 95 results were excluded in the screening and eligibility process. The reasons for exclusion were as follows; twenty articles did not involve any exercise or physical activity as a part of the intervention; twenty were only available as abstracts or protocols and an additional 15 were reviews; eight were not designed as randomized controlled trials (RCTs); four were reports or commentaries; four were published before 2004; three included participants under the age of 18 years; two had incomplete reporting of results; two included participants that were not posttreatment; one did not involve cancer patients, and finally one did not include biomarkers as an

outcome measure. After these exclusions, 15 articles remained which were then critically appraised and included for data extraction.[10-24]

Of these 15 articles, 13 RCTs were identified as three papers reported findings from the same intervention.[14,18,22] Ten RCTs were conducted in the United States of America. The remaining three originated from Australia,[11] the United Kingdom,[21] and the Republic of Ireland.[12] Breast cancer was by far the most investigated cancer with 11 of the 13 RCTs[10,12,14-24] reporting on it. One RCT included results from prostate and breast cancer survivors in the same intervention,[10] whereas two[11,13] investigated prostate cancer survivors only.

Almost all studies provided a detailed description of the exercise prescribed [Table 1]. Interventions included the following: Moderate intensity aerobic activity only;[10,12,13,15,17] moderate intensity aerobic and strength training,[11,16,19,21] resistance training only,[20,23,24] while three articles[14,18,22] were all on the same RCT investigating the effects of Tai Chi Chuan, a moderate form of weight bearing exercise, equivalent to walking. Moderate intensity for all studies was described as being between 70% and 85% maximum heart rate and/or perceived exertion at 11–13 on the Borg scale. One study[10] was a fully home based intervention, whereas the remaining studies incorporated supervised sessions as either the primary or partial form of delivery. The duration of the interventions ranged from between 2[12] to 24[23] months.

The total number of participants included in the studies varied. A third of the studies had over 100 participants,[10,11,16,23,24] another third had between 50 and 100 participants[13,15,17,20,21] with five studies having <30 participants in total.[12,14,18,19,23] Three studies did not state the ethnicity of the participants,[11,16,24] whereas the other studies reported a predominantly Caucasian population (70–100%). The mean age of the participants was between 50 and 60 years in 12 of the studies,[10,14-23] whereas two studies had an older mean of approximately 70 years[11,13] and one involved younger participants, with a mean of 48.12 years.[12] Details for the control group and other elements such as dietary/psychological support can be seen in Table 2.

As previously mentioned, the CASP questionnaire was used to determine the validity of each study's results. CASP uses six questions to evaluate the methodological quality and to determine if there is any bias in the studies. These questions investigate elements such as the reporting of; the randomization methodology, blinding of participants and/or assessors, similarity of groups at the start of the trial and whether all participants were accounted for at the conclusion. The studies included in this review all scored high validity with two[20,21] scoring 6 out of 6, while the remaining all scored 5/6.

All studies included survivors of cancer. However, studies defined posttreatment differently with some having

a minimum and maximum cut-off point for time after the completion of treatment, i.e., 1–30 months,[14,18,22] 2–6 months,[12] 4–36 months,[20] 3–18 months.[21] While others just reported a minimum time since treatment completion; at least 2 months post,[19] at least 3 months post,[16] at least 6 months post,[15,23] and at least 1 year post.[24] One study had a specific limit of diagnosis being within the previous 9 months,[10] whereas another had a longer window of within the previous 14 years.[17]

Seven of the studies mentioned the ACSM guidelines[5] and aimed their interventions towards obtaining the recommended standard of at least 150 min of moderate intensity aerobic activity a week.[10-13,15,19,24] The three studies of the same intervention investigating the effects of Tai Chi Chuan, reported the use of an ACSM accredited instructor as the administrator of the exercise sessions.[14,18,22] Similarly, two other studies used an ACSM certified fitness professional to implement the interventions despite only being focused on the effects of resistance training.[20,23] Ligibel *et al.*[16] placed an almost even emphasis on aerobic and strength training as participants received two supervised 50-min strength training sessions per week and were asked to complete 90 min of home-based aerobic exercise weekly. Pakiz *et al.*[17] followed the recommendations from the Institute of Medicine,[25] with a long-term goal to achieve an average of at least 1h/day of planned exercise at a moderate level of intensity. Scott *et al.*[21] devised an intervention that was a mixed aerobic and resistance program whereby participants attended three supervised sessions a week which consisted of 30 min aerobic exercise and 10–15 min of resistance training. This intervention used weight change as the primary outcome and had a strict hypocaloric diet element included.

Waltman *et al.*[23] was the only study not to report on weight or body mass index (BMI), each of the 14 other studies had changes in body composition as an outcome measure. Only two studies saw a significant reduction in BMI in the intervention groups ($P = 0.008$[10] and $P < 0.0001$[17]). Pakiz *et al.*[17] additionally reported significant changes to weight ($-6.8\%$ in intervention and $-0.3\%$ in control, $P < 0.0001$), waist circumference ($P < 0.05$), and percentage body fat ($P < 0.0001$) between baseline and 16 weeks. The other twelve studies did not find any significant effects on BMI,[11-16,18-22,24] although a decreasing trend was observed in all but two studies.[11,24]

Across the 15 articles, 34 different blood and urine biomarkers were reported, with insulin being the most commonly examined (eight studies). There was some similarity in the markers analyzed and certain patterns emerged which can be grouped as follows:
1. Insulin and glucose levels (including insulin resistance and glycated haemoglobin)
2. Inflammatory markers (IL-1b/IL-2/IL-6/IL-8/IL-10/IFN-γ/TNF-alpha/C-reactive protein [CRP]/cortisol)

McDermott, *et al*.: Biological markers as an outcome measure of exercise in cancer rehabilitation: A systematic review

**Table 1: Intervention summaries**

| References | Duration (months) | Intervention description | Intensity | Type | Frequency | Sample size |
|---|---|---|---|---|---|---|
| [10] | 10 | Home-based; every 6 weeks, participants received individualised newsletters (7 in total) designed to improve diet and exercise practices and provide feedback | Moderate | Aerobic | Individualised in order for participant to attain 150 min moderate intensity aerobic exercise per week | 489 |
| [11] | 12 | The sessions were led by an exercise physiologist in small groups | Moderate | Mixed programme of aerobic and resistance training | Twice a week supervised and twice a week home-based aerobic training for 6 months. Final 6 months was all home-based | 100 |
| [12] | 2 | Supervised by a physiotherapist and a research assistant | Moderate | Continuous, aerobic exercise using large muscle groups | Two classes per week and exercise in the home environment, starting with at least 1 other day and building up to 3 other days per week | 26 |
| [13] | 6 | Led by instructors; individual session was given where diet and physical activity goals were discussed. Then group session were carried out for 3 months with a monthly group booster session and progress calls made to the participant for the next 3 months | Moderate | Aerobic; brisk walking | Twelve 2.5–h group sessions conducted weekly over the first three months, then monthly group sessions and progress calls | 59 |
| [14,18,22] | 3 | Led by an ACSM certified health and fitness instructor | Moderate form of weight bearing exercise, equivalent to walking | 1 h Tai Chi Chuan session | 1 h three times a week for duration of the trial | 19 |
| [15] | 6 | Three times a week participant attended certified exercise trainer–supervised exercise and twice-weekly unsupervised exercise sessions | Moderate | Aerobic | Three supervised and two unsupervised exercise sessions a week | 75 |
| [16] | 4 | Supervised strength training and home-based cardiovascular training protocol. Groups of one to three women worked with a personal trainer during each of resistance training sessions | Moderate | Two supervised strength training sessions and 90 min of home-based aerobic exercise weekly | Two supervised weight training sessions and 90 min of home-based aerobic exercise weekly | 101 |
| [17] | 4 | Group sessions were provided weekly for 4 months, and follow-up monthly sessions through 12 months. The intervention sessions were led by trained investigators and research staff | Moderate | Regular planned aerobic exercise | The long-term goal was to achieve an average of at least 1 h/day of planned exercise at a moderate level of intensity | 85 |
| [19] | 3 | 6 weeks supervised (3 sessions for 2 weeks, 2 session for 2 weeks, 1 session for 2 weeks) led by an ACSM certified health and fitness instructor. Home-based but 1 face-to-face update and counselling session per week for final 6 weeks | Moderate | Walking and strength training using resistance bands | Goal was to gradually increase activity to 150 weekly minutes of at least moderate intensity exercise and 2 sessions per week on nonconsecutive days of resistance training | 28 |
| [20] | 12 | First 3 months led by an ACSM and/or National Strength and Conditioning Association certified fitness professional in small groups of 4 participants. For the next 3 months participants were expected to train unsupervised at the centre and keep a record. For the final 6 months participants were not required to record exercise sessions, although trainers continued tracking those who opted to continue to record sessions | Moderate | Resistance training | 1 h sessions, twice weekly for 13 weeks. Then the participants were expected to continue to train for an additional 13 weeks on their own and for the final 6 months they were not required to log activity but could continue with the programme if they pleased | 85 |

*Contd...*

**Table 1: Contd...**

| References | Duration (months) | Intervention description | Intensity | Type | Frequency | Sample size |
|---|---|---|---|---|---|---|
| [21] | 6 | Does not state what qualifications the leader of the session had | Moderate | Aerobic and resistance training | 3 weekly supervised exercise sessions for 6 months | 90 |
| [23] | 24 | Certified exercise trainers demonstrated exercises to subjects and made home or fitness centre visits to subjects every 2 weeks for 9 months and every 2 months for the remainder of the 24 months study | Moderate | Resistance training | For the first 9 months, participants exercised twice weekly for 30-45 min in their home. They were then given a stipend to use facilities at a fitness centre for months 10-24 | 249 |
| [24] | 12 | Certified exercise instructors were trained and supervised by the research team to deliver the exercise protocols. Home programs began after 1 month of supervised classes | Moderate to high bone loading forces according to ACSM guidelines; 60–70% of 1-RM for 1-3 sets of 8-12 repetitions | Resistance and/or impact exercise | Two supervised classes and one home-based session per week for 12 months. Each exercise session lasted 45-60 min | 106 |

ACSM=American College of Sports Medicine

3. The insulin-like growth factor (IGF) signaling system (IGF-I/IGF binding protein 1 [IGFBP-1]/IGFBP-3/IGF-II IGFB)
4. Lipids (total cholesterol/low-density lipoprotein/high-density lipoprotein [HDL]/triglycerides)
5. Sex hormones (testosterone/prostate specific antigen/sex hormone binding globulin [SHBG]/esterone estradiol)
6. Hormones (adiponectin/leptin)
7. Bone health (NTx/bone- specific alkaline phosphatase/serum osteocalcin, urinary deoxypyrodinoline cross-links).

The detailed findings for each of the biomarkers can be found in Table 3. Exercise was shown to have a significant effect on several biomarkers Including the following;

### Insulin and insulin resistance

Ligibel *et al.*[16] found that fasting insulin concentrations decreased significantly in the exercise group pre- and post-intervention ($P = 0.03$); however, when compared to the control group, this did not reach significance ($P = 0.07$). Janelsins *et al.*[14] found that there was a significant main effect for insulin ($P = 0.099$) as levels remained relatively stable in the intervention but increased in the control group. Ligibel *et al.*[16] also found that there was a marginally significant improvement in insulin resistance in the exercise group after the 16-week exercise intervention ($P = 0.05$), with no significant change in controls ($P = 0.81$).

### Total cholesterol and high-density lipoprotein cholesterol

Total cholesterol was measured in four studies with two reporting significant changes.[11,21] It should be noted however that the change seen in the exercise group by one study[21] was a reduction whilst an increase was reported by the other,[11] therefore giving inconclusive results.

Similar results were seen for HDL, as Scott *et al.*[21] and Galvão *et al.*,[11] were the only two of four studies to show significant results. The results were inconclusive again as one study[21] showed an increase in the control group compared to a stabilization in the intervention group, whereas an increase was observed in the exercise group by the other.[11]

### Leptin

Scott *et al.*[21] also found that leptin was significantly different ($P = 0.005$) between groups, as an increase was seen in the control group, while the exercise group levels decreased postintervention.

### Insulin-like growth factor-II and insulin-like growth factor binding protein-3

Five studies measured IGFBP-3; however, Schmitz *et al.*[20] was the only RCT to find significant results. As the control group received the intervention for 6 months after a 6 month delayed period, information was available from this group which showed the levels of IGFBP-3 and also IGF-II were significantly decreased after 6 months of training compared with the change experienced during 6 months of not training. This was the only study to measure IGF-II and found that the intervention group significantly decreased their levels ($P = 0.02$) after 6 months of weight training.[20]

### Osteocalcin

Serum osteocalcin was investigated as a measure of bone turnover in one study[24] as increased levels are associated with metabolic bone diseases such as osteoporosis and bone metastases. Significant differences were observed between the control and intervention groups, with levels remaining stable in the intervention group but increasing in the control group.[24]

McDermott, *et al.*: Biological markers as an outcome measure of exercise in cancer rehabilitation: A systematic review

**Table 2: Details of other intervention elements and control group description**

| References | Cancer type | Other elements | Control group |
|---|---|---|---|
| [10] | Breast and prostate cancer survivors | Information relating to fruit and vegetable consumption, low-fat dietary practices, exercise and smoking cessation were distributed | The surveys for control participants assessed the perceived helpfulness of the brochures. Control participants received an initial workbook and subsequent materials which were available in the public domain on; exercise, fruit/vegetable consumption, smoking cessation and low-fat dietary practices |
| [11] | Prostate cancer survivors | Both the intervention and control groups were encouraged to maintain customary dietary patterns | The control group received a pedometer and a modified educational booklet with a general recommendation to perform 150 min per week of moderate physical activity during the entire 12-months period |
| [12] | Breast cancer survivors | Both the intervention and control groups were encouraged to maintain customary dietary patterns | The control group did not engage in a structured exercise programme but were offered an exercise advice session following the final assessment |
| [13] | Prostate cancer survivors | Participants were given daily "homework" that consisted of cooking, physical activity and stress reduction activities. The diet portion of the intervention was focused on goals related to decreasing meat and dairy consumption while increasing consumption of whole grains, soybeans and soybean products, other beans and vegetables | No attempt was made to limit control participants' use of psychosocial care available in the community or to national educational or supportive resources. Those assigned to the control were given the option to take the intervention, free of charge following their participation as a control for 6 months |
| [14,18,22] | Breast cancer survivors | No other elements stated | The control group received support therapy by a trained counsellor and exercise psychology graduate student with emphasis on behavioural coping strategies, cohort support, and group unity. Participants were instructed not to change their pattern of physical activity in any manner for the duration of the intervention |
| [15] | Breast cancer survivors | Participants were advised to maintain their current dietary habits | Women in the usual care group were instructed to continue with their usual activities. Participants were free to exercise of their own accord and received the exercise program and training materials at the end of the study |
| [16] | Breast cancer survivors | All participants were asked to avoid changes in dietary habits for weight loss purposes for the duration of the study | The control group received routine care for 16 weeks and were then offered a consultation with an exercise trainer at the end of the control period |
| [17] | Breast cancer survivors | The intervention included behavioural and cognitive strategies for implementing dietary modification as well as increasing physical activity. The main goal of the dietary guidance component was to promote a reduction in energy intake relative to expenditure (an energy deficit of 500–1000 kcal/day), by individualized diet modification | They were provided only general contact (monthly check-up calls, holiday and seasonal cards, and mailed communications) without specific reference to weight management topics through a 12-month period of data collection. Following that period, they were provided all intervention materials and a facilitated discussion was offered in the format of a 2-day seminar |
| [19] | Breast cancer survivors | Participants were advised to maintain their current dietary habits however diet was monitored via diet records in order to account for this when analysing weight loss results | Because the focus of the intervention was behaviour change rather than exercise efficacy, the usual care control group received written materials from the American Cancer Society, which included general information about physical activity and nutrition after a cancer diagnosis but did not include specific recommendations regarding exercise behaviour |
| [20] | Breast cancer survivors | Participants were advised to maintain their current dietary habits and to not make any changes in other elements of their exercise program (e.g., walking, bicycling, and swimming) | The delayed treatment group served as a no exercise parallel comparison group from months 0 to 6 and trained from months 7 to 12. Protocol was same as intervention; they met twice a week for 1 hour for 13 weeks supervised by ACSM and/or National Strength and Conditioning Association certified fitness professional in small groups of 4 participants |
| [21] | Breast cancer survivors | Intervention group received one-to-one individualised dietary advice and written information. The goal was to reduce total daily calorie intake to 600 kcal below their calculated energy requirements to induce an estimated steady weight loss of up to 0.5 kg each week | They received a healthy eating booklet which also included brief advice on keeping active |
| [23] | Breast cancer survivors | Both groups received 24 months of 1200 mg of calcium and 400 IU of Vitamin D daily and 35 mg of risedronate weekly | Received medication but no exercise intervention received |

*Contd...*

**Table 2: Contd...**

| References | Cancer type | Other elements | Control group |
|---|---|---|---|
| [24] | Breast cancer survivors | Participants were advised to maintain their current dietary habits. Diet and exercise outside of the intervention was assessed via questionnaires | Participants in the control group performed a series of whole body stretching and relaxation exercises in a seated or lying position. Two supervised classes and one home-based session per week for 12 months. Each exercise session lasted 45–60 min |

ACSM=American College of Sports Medicine

## DISCUSSION

As seen in the results section, the markers identified in this review suggest that the overall hypothesized effect that exercise may have on biochemistry in the body is possibly through three main systems; the metabolic system (insulin/glucose control, cholesterol/lipids); the inflammatory system (CRP, TNF-alpha, and IL-6); and the hormonal system specifically sex hormones (testosterone and estrogen). These three pathways, along with the addition of markers associated with bone health, were the most commonly investigated systems. This is reflective of the suggested causation mechanisms linking obesity and physical inactivity to cancer. In a systematic review completed by Lynch,[26] adiposity accumulated through sedentary behavior was suggested as an independent contributor to cancer, causing; metabolic dysfunction (increases in insulin and glucose); inflammation (increases in TNF-alpha, IL-6, and CRP); and altering sex hormones (increases in androgen and estrogen and decreases in SHGB).[26] The National Cancer Institute[27] also names these same three pathways in the association between obesity and cancer. As physical activity and diet are the main modifiable components to improve overall health by optimizing the body's systems and reducing fat, it is therefore reasonable to hypothesize that exercise may positively affect these systems and consequently elicit beneficial outcomes.

The results from this review, however, are insufficient to prove that short-term exercise interventions for cancer survivors can alter these mechanisms. Out of the nine studies that measured insulin as an outcome measure, only two found any significant results. Ligibel *et al.*[16] saw a decrease in the exercise group, whereas Janelsins *et al.*[14] reported exercise group levels remaining stable with an increase in the control group. Janelsins *et al.*[14] was however a pilot study with 19 participants and so the results are preliminary. While Ligibel *et al.*[16] was powered greater with a larger sample size of 82, the study was restricted to women with a BMI greater than 25 kg/m$^2$ and/or a body fat percentage of more than 30%. Therefore, these results are inconclusive.

Insulin is also involved in another system which has come under scrutiny in the development of cancer risk; the IGF signalling system. This is due to the fact that insulin plays a central role in cellular growth, differentiation, and proliferation.[28] IGF-I circulates in association with specific BPs[29] including IGFBP-1,-2,-3, and-4. Six studies (from four interventions) included IGF-1, IGFBP-1 and -3 measures

as part of their outcomes; however, only two found any changes postintervention. In their 6 month weight training intervention with a 6 month follow-up, Schmitz *et al.*[20] found that IGFBP-3 and IGF-II levels significantly decreased in the delayed treatment group after 6 months of training compared with the change experienced during the 6 months of not training ($P = 0.03$ and $P = 0.02$, respectively). Similarly, another 6 month moderate intensity aerobic intervention, study[15] reported significant differences between groups in IGF-I and IGFBP-3 levels. IGF-I decreased in the exercise group and increased in the control group, resulting in a significant difference postintervention ($P = 0.026$). Levels of IGFBP-3 decreased in the intervention group versus an increase in the control group, resulting in an overall between-group difference ($P = 0.006$). It should be noted that statistical power was limited in both of these studies and therefore results can only be considered as preliminary.

Maintaining healthy cholesterol levels is extremely important for physiological health. The factors pertaining to the metabolic syndrome include the presence of high triglycerides ($\geq 150$mg/dL) and low levels of HDL (men <40mg/dL, women <50mg/dL).[30] An elevation of cholesterol in the blood is very common in those who are overweight or obese and has been linked to many cancers including breast,[31] colorectal,[32] and prostate.[33] Out of four studies that measured cholesterol and lipids, only two[11,21] reported any significant findings. Both found favorable results for total cholesterol but in different ways; a significant reduction was seen in the intervention group by one study,[21] while the change seen by the other[11] was caused by a significant increase in intervention group. For HDL levels, Scott *et al.*[21] reported that levels stayed relatively stable in the intervention group whereas the control group levels rose causing a significant difference, this is in contrast to the significant increase found in the exercise group by Galvão *et al.*[11] A possible explanation for the results seen by Scott *et al.*,[21] may be that the control group levels were lower (but not significantly different) to the exercise group at baseline (1.60 [1.36, 1.80] vs. 1.47 [1.19, 1.74]).

The only other RCT to find any significant changes to biological marker results was Winters-Stone *et al.*[24] In their 12 month intervention involving impact and resistance exercises, serum osteocalcin significantly changed as levels remained stable in the intervention but increased in the control group. There were no common trends between any of the seven interventions that found significant results with

McDermott, *et al.*: Biological markers as an outcome measure of exercise in cancer rehabilitation: A systematic review

**Table 3: Biological marker results**

| Biomarker | Number of studies | Results |
|---|---|---|
| Insulin | 9 | Janelsins *et al.*[14] found a significant main effect for insulin (*P*=0.099) as levels remained relatively stable in the intervention group (mean change=1.41; Cohen's *d*=0.20) but increased in the control group (mean change=15.02; Cohen's *d*=0.66)<br>Four studies showed no changes,[11,12,20,21] while three found borderline significant results; Sprod *et al.*,[22] saw that there was a statistical trend toward an increase among the control participants (*P*=0.08), but not among the intervention (*P*=0.56); Jones *et al.*[15] observed a reduction in insulin levels among exercisers and an increase among controls (*P*=0.089); and Ligibel *et al.*[16] found that fasting insulin concentrations decreased significantly in the exercise group pre- and post-intervention (*P*=0.03); however, when compared to the control group, this did not reach statistical significance (*P*=0.07)<br>Christy *et al.*[10] were underpowered to detect significant differences |
| IL-6 | 7 | None of the seven studies found significant results<br>Three studies reported trends for increases in the intervention group levels compared to the control,[14,15,19] while one noted a reduction in intervention group IL-6 levels (*P*=0.06) between baseline and 16 weeks[16] |
| Glucose | 6 | No significant results were seen for 5 of the 6 studies,[11,12,16,20,21] while one only found that there was a statistical trend for an increase among the intervention but not the control participants[22] |
| IGF-1/IGFBP-1 IGFBP-3 | 6 | IGFBP-3 significantly decreased in the delayed treatment group after 6 months of training compared with the change experienced during the 6 months not training (*P*=0.03)[20]<br>IGF-I decreased in the exercise group and increased in the control, resulting in a significant difference between the groups postintervention (*P*=0.026).[15] Similarly, levels of IGFBP-3 decreased in the intervention group versus an increase in the control group, resulting in an overall between-group difference (*P*=0.006).[15]<br>Schmitz *et al.*[20] found no intervention effects for IGF-1. Three studies reported no significant changes over time in either group for IGF-1, IGFBP-1, or IGFPB-3.[14,21,22] Study[18] also did not find any significant results for IGFBP-3 |
| Total cholesterol/LDL/HDL | 4 | Total cholesterol<br>Significant reduction seen in intervention group (*P*=0.046)[21]<br>Significant increase in total cholesterol in intervention group comparison to the control group (*P*=0.014)[11]<br>Christy *et al.*[10] were underpowered to detect significant changes however the intervention group saw a trend for a greater decrease in plasma cholesterol that the control<br>HDL cholesterol<br>HDL stayed relatively stable in the intervention group whereas the control group level rose causing a significant difference (*P*=0.015)[21]<br>Significant increase in the exercise group (*P*=0.001)[11]<br>No significant changes seen by study[11] and study[10] was underpowered<br>LDL cholesterol<br>No significant changes seen by any study of the 4 studies[10-12,21] |
| IL-8 | 4 | There were no differences noted for IL-8 in three of the studies[17,18,22] and only small to medium nonsignificant negative effect sizes were noted for IL-8 to IL-10 ratios by Rogers *et al.*,[19] |
| CRP | 4 | CRP levels in the exercise group decreased postintervention, while it increased by in the control group; however, changes were not found to be significant between groups (*P*=0.07 and *P*=0.69, respectively)[12]<br>No significant changes were seen postintervention between groups in two studies (*P*=0.80[15] and *P*=0.73[21]), while the other was underpowered[10] |
| TNF-α | 3 | The only study to find significant results saw a decrease at 16 weeks for the control group (*P*<0.05)[17] |
| TG/glycated hemoglobin | 2 | Differences were not observed for TG or glycated haemoglobin in either study[11,12] |
| Leptin | 2 | The intervention group significantly decreased leptin levels (*P*=0.005) compared to the control (*P*=0.005)[21]<br>While not significant, Rogers *et al.*[19] found that the intervention was associated with a large effect size reduction in leptin compared with the control |
| Insulin resistance | 2 | Marginally significant improvement in insulin resistance in the exercise group after the 16-week exercise intervention (*P*=0.05), with no significant change in controls (*P*=0.81)[16]<br>Insulin and the HOMA index were both severely skewed and therefore not reported by Schmitz, *et al.*,[20] |
| IL-2/IFN-γ | 2 | IL-2 and IFN-γ increased in the control group and decreased in the intervention group, although the main effect was not significant for either IL-2 (*P*=0.369) or IFN-γ (*P*=0.831)[14]<br>Peppone *et al.*[18] only reported the relationship of IL-2 as being negatively correlated with the observed increase in bone formation |
| IL-1b | 2 | IL-1β was not detectable in ≥95% of the samples and therefore statistical comparisons were not performed.[19] Peppone *et al.*,[18] also do not report the results of IL-1b |
| Testosterone | 2 | Differences were not observed for testosterone in either study[11,21] |

*Contd...*

**Table 3: Contd...**

| Biomarker | Number of studies | Results |
|---|---|---|
| PSA | 2 | No significant changes for PSA however approximately half (48% overall; 50% in intervention group) of the participants experienced a decrease or no change in PSA at 3 months[13] Differences were not observed by Galvao *et al.*[11] |
| NTx/BSAP | 2 | A greater, though not significant, increase in bone formation was reported in the intervention group versus the control (P=0.17).[18] The intervention group also exhibited a greater, nonsignificant decline in bone resorption than the control group (P=0.14).[18] Waltman, *et al.*[23] reported differences between the exercise and control group; however, they were not significant as the exercise group had a greater mean decrease in Alkphase B and also a greater mean decrease in serum NTx than the control group |
| IGF-II/IGFBP-2 | 1 | IGF-II levels significantly decreased in both groups after 6 months of weight training when compared with a concurrent comparison group or using within person controls (P=0.02 for both comparisons).[20] Pearson's correlation coefficients for baseline and 6-month values of log of IGF-II, IGFBP-2 were 0.88 and 0.82, respectively[20] |
| Free IGF-1 | 1 | Peppone *et al.*[18] does not report any results for free IGF-1 |
| IL-10 | 1 | The statistical significance could not be analyzed[19] |
| Cortisol | 1 | There were no significant changes evident over time in either group for cortisol[22] |
| Total/HMW adiponectin | 1 | The statistical significance could not be analysed due to lack of power[10] |
| VEGF | 1 | No significant differences were noted for VEGF[17] |
| SHBG | 1 | No significant results were found for SHBG[21] |
| Esterone estradiol | 1 | No significant results were found for esterone estradiol[21] |
| Osteocalcin/urinary deoxy-pyrodinoline cross-links | 1 | Serum osteocalcin remained relatively constant in the intervention group, however an increase was seen in the control group which proved to be significantly different (P=0.01)[24] There was also a greater, though nonsignificant decrease in deoxypyrodinoline cross-links in the intervention versus control (P=0.22)[24] |

SHBG=Sex hormone-binding globulin, VEGF=Vascular endothelial growth factor, PSA=Prostate-specific antigen, IGF=Insulin-like growth factor, IGFBP=Insulin-like growth factor binding protein, IL=Interleukin, IFN-γ=Interferon gamma, BSAP=Bonespecific alkaline phosphatase, HOMA=Homeostasis model assessment, TG=Triglycerides, CRP=C-reactive protein, LDL=Low-density lipoprotein, HDL=High-density lipoprotein, HMW=High-molecular weight

regard to length of intervention or type of exercise prescribed. Six included breast cancer and one included prostate cancer survivors.[11] Three were of 12 months duration,[11,20,24] whereas two were 6 months,[15,19] one was 4 months,[16] while another was 3 months in duration.[14] Only one study[21] controlled for diet as the other six instructed participants to keep their regular habitual diet. This may indicate that interventions solely focused on exercise and between 6 and 12 months in duration may be the most appropriate in order to establish changes in biological markers.

A limitation of the studies included in this review was the lack of statistical power due to the small sample sizes. Seven out of the 13 RCTs were underpowered due to the small sample sizes.[10,12-15,18-20,22] Although one study[10] had a large sample size of 498, blood samples were only collected from a 23% subset, rendering it underpowered to detect significance. Of the remaining studies, one[17] used a 2:1 intervention-to-control ratio to provide sufficient statistical power for the main participants (44 intervention and 24 control). Even though the desired number of participants were recruited to provide an adequately powered comparison, due to the small sample size, the findings should still be considered exploratory.[17] One study[11] was powered for $n = 100$ ($n = 50$ in each group), which is the number of participants that was recruited however 22 participants dropped out, affecting the statistical power. Two further studies were arguably underpowered as they failed to recruit a sufficient target sample size. Due to modest retention rates (62%), one study[24] fell three participants short of the estimated sample size. This meant that the results can still be regarded as potentially underpowered; however, the authors argue that as there were no borderline $P$ values, the possibility of having an inadequate sample size was not questioned. Similarly, Scott *et al.*,[21] fell just seven participants short of the target of 90 participants. Of the two remaining studies, one[23] exceeded the recruitment target by five participants (110 exercise; 113 control), while the other[16] was also adequately powered (40 exercise; 42 control); however, it must be noted that this study only included sedentary, overweight participants.

None of the studies met the requirements that Rogers *et al.*[19] alludes to, of needing at least 400 participants in each arm in order to detect an effect size of 0.2 with a power of 80 and $P < 0.05$.[34] Another limitation is the fact that only two studies specifically excluded participants taking dietary supplements,[13,21] while one study[23] prescribed calcium and Vitamin D to participants and another measured supplementation.[24] None of the other 11 studies reported use of supplementary treatments. The use of dietary supplements is still popular among cancer patients after diagnosis.[35] Given the potential effect of simultaneous treatments on blood biomarkers, future studies should at least record and report such intake. Finally, as the majority of the studies included breast cancer survivors, this limits the ability to apply results across other types of cancer populations. Thus, it is difficult due to insufficient evidence to draw any conclusions regarding the association between exercise and change in biological markers in cancer survivors.

## CONCLUSIONS

In the studies selected for this review, 35 different biomarkers were analysed across different physiological systems including the inflammatory, hormonal, metabolic, and skeletal systems. Insulin, IL-6, and glucose were the 3 most commonly investigated markers but despite the diverse range and number of markers in this review, only seven (insulin, IGFBP-3, IGF-II, total cholesterol, HDL cholesterol, leptin, and osteocalcin) were shown to alter with an exercise intervention. The results found for these markers were insufficient to draw any conclusions due to small sample sizes. Larger RCTs of at least 800 participants need to be implemented in order to be adequately powered to detect changes in biological markers.

There was an extremely limited population of cancer types evident with breast being by far the most investigated cancer (13 of the 15 studies). Therefore the information from this review cannot be generalized for all-type cancer populations. Surprisingly, the duration of the intervention does not seem to affect results as four of the seven studies to find significant differences were of 6 months or less duration. There were many varieties of exercise interventions implemented by researchers regarding their duration, type of exercise, frequency, and delivery; however, almost all alluded to the ACSM guidelines. Overall, the ACSM does make the explicit recommendation to simply encourage survivors to "avoid inactivity" as "some physical activity is better than none."[5] Targeting cancer survivors posttreatment can be an effective time point as they are often highly motivated to make positive lifestyle changes to improve their treatment outcomes, quality of life and overall survival.[36]

In conclusion, from the information provided from 15 studies, exercise was proven to be a safe, acceptable, and effective method of intervention for certain health outcomes; however, more research is warranted in order to claim any clear conclusions of the biochemical effect of exercise on cancer survivors.

### Financial support and sponsorship

### Conflicts of interest
There are no conflicts of interest.

## REFERENCES

1.  Maddams J, Utley M, Møller H. Projections of cancer prevalence in the United Kingdom, 2010-2040. Br J Cancer 2012;107:1195-202.
2.  Naci H, Ioannidis JP. Comparative effectiveness of exercise and drug interventions on mortality outcomes: Metaepidemiological study. Br Med J 2013;347:5577.
3.  Campbell A, Foster J, Stevinson C, Cavill N. The Importance of Physical Activity for People Living with and Beyond Cancer – A Concise Evidence Review. Macmillan Cancer Support; 2012. Available from: http://www.macmillan.org.uk/Documents/AboutUs/Commissioners/Physicalactivityevidencereview.pdf. [Last cited on 2015 Apr 16].
4.  Department of Health, Physical Activity, Health Improvement and Protection. Start Active, Stay Active: A Report on Physical Activity from the Four Home Countries' Chief Medical Officers. GOV.UK; 2011. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216370/dh_128210.pdf. [Last cited on 2015 Apr 16].
5.  Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409-26.
6.  Löf M, Bergström K, Weiderpass E. Physical activity and biomarkers in breast cancer survivors: A systematic review. Maturitas 2012;73:134-42.
7.  McTiernan A, Schwartz RS, Potter J, Bowen D. Exercise clinical trials in cancer prevention research: A call to action. Cancer Epidemiol Biomarkers Prev 1999;8:201-7.
8.  Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg 2010;8:336-41.
9.  Critical Appraisal Skills Programme (CASP). CASP Randomised Controlled Trial Checklist. CASP UK; 2014. Available from: http://www.media.wix.com/ugd/dded87_40b9ff0bf53840478331915a8ed8b2fb.pdf. [Last cited on 2015 Mar 17].
10.  Christy SM, Mosher CE, Sloane R, Snyder DC, Lobach DF, Demark-Wahnefried W. Long-term dietary outcomes of the FRESH START intervention for breast and prostate cancer survivors. J Am Diet Assoc 2011;111:1844-51.
11.  Galvão DA, Spry N, Denham J, Taaffe DR, Cormie P, Joseph D, et al. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. Eur Urol 2014;65:856-64.
12.  Guinan E, Hussey J, Broderick JM, Lithander FE, O'Donnell D, Kennedy MJ, et al. The effect of aerobic exercise on metabolic and inflammatory markers in breast cancer survivors – a pilot study. Support Care Cancer 2013;21:1983-92.
13.  Hébert JR, Hurley TG, Harmon BE, Heiney S, Hebert CJ, Steck SE. A diet, physical activity, and stress reduction intervention in men with rising prostate-specific antigen after treatment for prostate cancer. Cancer Epidemiol 2012;36:e128-36.
14.  Janelsins MC, Davis PG, Wideman L, Katula JA, Sprod LK, Peppone LJ, et al. Effects of Tai Chi Chuan on insulin and cytokine levels in a randomized controlled pilot study on breast cancer survivors. Clin Breast Cancer 2011;11:161-70.
15.  Jones SB, Thomas GA, Hesselsweet SD, Alvarez-Reeves M, Yu H, Irwin ML. Effect of exercise on markers of inflammation in breast cancer survivors: The Yale exercise and survivorship study. Cancer Prev Res (Phila) 2013;6:109-18.
16.  Ligibel JA, Campbell N, Partridge A, Chen WY, Salinardi T, Chen H, et al. Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. J Clin Oncol 2008;26:907-12.
17.  Pakiz B, Flatt SW, Bardwell WA, Rock CL, Mills PJ. Effects of a weight loss intervention on body mass, fitness, and inflammatory biomarkers in overweight or obese breast cancer survivors. Int J Behav Med 2011;18:333-41.
18.  Peppone LJ, Mustian KM, Janelsins MC, Palesh OG, Rosier RN, Piazza KM, et al. Effects of a structured weight-bearing exercise program on bone metabolism among breast cancer survivors: A feasibility trial. Clin Breast Cancer 2010;10:224-9.
19.  Rogers LQ, Fogleman A, Trammell R, Hopkins-Price P, Vicari S, Rao K, et al. Effects of a physical activity behavior change intervention on inflammation and related health outcomes in breast cancer survivors: Pilot randomized trial. Integr Cancer Ther 2013;12:323-35.

20. Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. Cancer Epidemiol Biomarkers Prev 2005;14:1672-80.

21. Scott E, Daley AJ, Doll H, Woodroofe N, Coleman RE, Mutrie N, *et al.* Effects of an exercise and hypocaloric healthy eating program on biomarkers associated with long-term prognosis after early-stage breast cancer: A randomized controlled trial. Cancer Causes Control 2013;24:181-91.

22. Sprod LK, Janelsins MC, Palesh OG, Carroll JK, Heckler CE, Peppone LJ, *et al.* Health-related quality of life and biomarkers in breast cancer survivors participating in Tai Chi Chuan. J Cancer Surviv 2012;6:146-54.

23. Waltman NL, Twiss JJ, Ott CD, Gross GJ, Lindsey AM, Moore TE, *et al.* The effect of weight training on bone mineral density and bone turnover in postmenopausal breast cancer survivors with bone loss: A 24-month randomized controlled trial. Osteoporos Int 2010;21:1361-9.

24. Winters-Stone KM, Dobek J, Nail L, Bennett JA, Leo MC, Naik A, *et al.* Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: A randomized, controlled trial. Breast Cancer Res Treat 2011;127:447-56.

25. Trumbo P, Schlicker S, Yates AA, Poos M; Food and Nutrition Board of the Institute of Medicine, the National Academies. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. J Am Diet Assoc 2002;102:1621-30.

26. Lynch BM. Sedentary behavior and cancer: A systematic review of the literature and proposed biological mechanisms. Cancer Epidemiol Biomarkers Prev 2010;19:2691-709.

27. National Cancer Institute. Obesity and Cancer Risk Available from: http://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet. [Last updated on 2012 Jan 03; Last cited on 2015 May 20].

28. Ali O, Cohen P, Lee KW. Epidemiology and biology of insulin-like growth factor binding protein-3 (IGFBP-3) as an anti-cancer molecule. Horm Metab Res 2003;35:726-33.

29. Koziris LP, Hickson RC, Chatterton RT Jr., Groseth RT, Christie JM, Goldflies DG, *et al.* Serum levels of total and free IGF-I and IGFBP-3 are increased and maintained in long-term training. J Appl Physiol 1999;86:1436-42.

30. McArdle WD, Katch FI, Katch VL. Exercise Physiology: Nutrition, Energy, and Human Performance, International edition. 7th ed. Philadelphia, PA, London: Wolters Kluwer/Lippincott Williams and Wilkins; c2010.

31. Kaiser J. Cancer. Cholesterol forges link between obesity and breast cancer. Science 2013;342:1028.

32. Herbey II, Ivankova NV, Katkoori VR, Mamaeva OA. Colorectal cancer and hypercholesterolemia: Review of current research. Exp Oncol 2005;27:166-78.

33. Braun S, Bitton-Worms K, LeRoith D. The link between the metabolic syndrome and cancer. Int J Biol Sci 2011;7:1003-15.

34. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.

35. Greenlee H, Kwan ML, Ergas IJ, Strizich G, Roh JM, Wilson AT, *et al.* Changes in vitamin and mineral supplement use after breast cancer diagnosis in the Pathways Study: A prospective cohort study. BMC Cancer 2014;14:382.

36. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, *et al.* Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:243-74.