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Exercise and the IGF axis in oncology

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Abstract

Exercise and physical activity have been shown to reduce the risk of many common cancers and strongly influence tumour biology. A cause-effect mechanism explaining this relationship is dependent on cellular pathways that can influence tumour growth and are exercise-responsive. The insulin-like growth factor (IGF) axis is reported to promote the development and progression of carcinomas through cellular signalling in cancerous tissues. This review summarises the physiological basis of the role of the IGF axis in oncology and the influence of exercise on this process. We examined the effects of exercise prescription on the IGF axis in cancer survivors by evaluating the current scope of the literature. The current research demonstrates a remarkable heterogeneity and inconsistency in the responses of the IGF axis to exercise in breast, prostate and colorectal cancer survivors. Finally, this review presents an in-depth exploration of the physiological basis and mechanistic underpinnings of the seemingly disparate relationship between exercise and the IGF axis in oncology. Whilst there is currently insufficient evidence to categorise the effects of exercise prescription on the IGF axis in cancer survivors, the inconsistency of results suggests a multifaceted relationship, the complexities of which are considered in this review.
1. **Physiological basis of the insulin-like growth factor axis in oncology**

The weight of epidemiological data shows that physical activity is associated with a decreased risk in the incidence of many common cancers (1-5). Distillation of these findings suggests a cause-effect relationship between exercise and carcinoma development and progression (6). Underpinning this relationship are physiologically plausible pathways that are responsive to exercise and capable of influencing cellular processes associated with carcinogenesis.

The insulin-like growth factor (IGF) axis is a potentially significant mechanism that explains, at least in part, the inverse relationship between exercise and risk of cancer incidence (7-9). A full physiological review of the IGF axis is beyond the scope of this review, those interested are referred to the work of Annunziata et al. (10). Briefly, the IGF axis consists of two specific ligands, (i) insulin-like growth factor-1 (IGF-1) and (ii) IGF-2, which interact with their primary cell surface tyrosine kinase receptor, the IGF-1 receptor (IGF-1R). Activation of the IGF-1R by IGF-1 or IGF-2 is achieved through endocrine mechanisms, primarily of hepatic origin but also through paracrine and autocrine mechanisms produced in extra-hepatic tissues (11). Transphosphorylation of the IGF-1R by the ligands IGF-1 and IGF-2 initiates cellular signalling through the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways, which facilitates DNA synthesis, cellular survival, proliferation and differentiation in the target cell (8, 12). While these processes of cellular signalling and receptor activation are central to the development and growth of many tissues (13), activation of the IGF-1R and subsequent signalling in cancerous cells is thought to promote tumorigenesis and progression (14). The strength of association between IGF-1R signalling and carcinogenesis is such that pharmacological methods of IGF-1R signalling ablation are being actively pursued through pre-clinical and clinical trials as potential cancer treatments (14, 15).
In circulation, the degree of IGF-1R activation in cancerous tissues is dependent on systemic levels of the IGF ligands. Indeed meta-analytical data show that elevated levels of systemic IGF-1 are associated with an increase in colorectal (16), prostate (17, 18), and pre-menopausal breast cancer (18) risk. Whilst the epidemiological evidence is inconsistent, several pre-clinical in-vitro (19-22) and in-vivo (23, 24) tumour models have strengthened the causal relationship between elevated IGF-1 concentrations and increased tumour growth and development. The bioactivity and subsequent mitogenicity of the IGF ligands in carcinous cells is modulated by a number of high affinity IGF binding proteins (IGFBP-1 to IGFBP-6). IGFBPs competitively bind to IGF-1 and IGF-2, reducing the capability of these ligands to bind with their cognate receptors (25). Whilst IGFBPs are thought to generally inhibit the actions of the IGF ligands as a result of this competitive binding, the IGFBPs also exhibit IGF-1R and ligand-independent inhibitory effects on cellular growth (26). The role of IGFBPs however is not unidirectional; in some circumstances the IGFBPs have been shown to exhibit IGF ligand-potentiating effects, therefore increasing the tumorigenic potential of these ligands. The mitogenic roles of IGFBPs are yet to be confirmed but likely related to binding substantially increasing IGF ligand half-life and the subsequent proteolysis of the binding protein in the tumour microenvironment enhancing delivery of the IGF ligands to the IGF-1R (11, 26).

Reducing IGF-1R signalling in carcinogenic tissues is an important focus within the oncology field. Exercise training is hypothesised to elicit physiological changes in systemic IGF ligand and binding protein bioavailability, which may indirectly influence IGF-1R signalling. Two previous systematic reviews have broadly investigated the effect of exercise interventions on a range of biomarkers associated with breast cancer (27) and all cancer types (28) which included the IGF axis. Both reviews were limited in the analysis of the IGF axis due to the breadth of biomarker systems investigated in these reviews. This prevented an extensive exploration of the complexities of the IGF axis response to exercise, specifically in oncological populations. Both the rapid development of exercise oncology biomarker
research and growing interest in the clinical utility of strategies to promote IGF-IR inhibition in cancerous tissues necessitates a specific and in-depth analysis of both the physiology of this relationship and the determining factors that can maximise the anti-carcinogenic effect of exercise. The purpose of this review was to summarise the extant knowledge of the effects of exercise prescription (frequency, intensity, duration and modality) on the IGF axis in populations with a history of cancer. This review offers future perspectives for research in this field, by considering the physiological basis and mechanisms underpinning the relationship between exercise and the IGF axis on carcinogenic progression.

2. Search strategy

To define the current literature, searches were conducted in August 2014 utilising the following databases: PubMed, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), SCOPUS, SPORTDiscus and the Physiotherapy Evidence Database (PEDro). Search functions were generated using free-text terms according to the four central tenets of the inclusion criteria and were amalgamated using Boolean operators and truncation functions: [study design: trial, random*, intervention, study, control*] AND [population: adult*, individual*, participant*, patients, human*, subjects] AND [intervention: exercise*, training, weight*, resistance*, aerobic*, strength*, muscular*, endurance, walk*, running, cycling] AND [primary outcome: insulin*like*growth*factor*, IGF*, IGF*binding*protein*]. The inclusion criteria were: (i) design: randomised controlled trials, controlled trials and single-group intervention studies; (ii) population: men and/or women aged ≥18 years old, previously diagnosed with cancer but not currently undergoing any form of surgery, chemotherapy or radiation therapy; (iii) intervention: structured (prescription according to one or more of mode, frequency, intensity and/or dose) exercise interventions only, not trialled in conjunction with other interventions (e.g. dietary intervention); (iv) outcome: systemic in-vivo (human) measurement of the IGF axis prior to and following an exercise intervention. Only full-text, English language articles were included.
3. Current scope of the IGF axis response to exercise in oncology

The results of the search process are detailed in Figure 1. A total of 4251 articles were retrieved from database searching (n=4250) and from the literature of an author contained within the reference list of an included article (n=1). A total of seven articles satisfied the inclusion criteria (29-35); five randomised controlled trials (29, 31, 32, 34, 35) and two single-group intervention studies (30, 33). Four studies were conducted in breast cancer survivors (29, 31, 32, 35), two studies in populations with prostate cancer (30, 34) and one study in colorectal cancer survivors (33). All studies measured IGF-1, with all but one (30) also measuring its principle binding protein IGFBP-3. Four of the seven studies also assessed additional components of the IGF axis with IGF-2 measured in two studies (29, 35), IGFBP-1 measured in four studies (29, 32, 33, 35) and IGFBP-2 measured in one study (35). Only two studies (30, 34) assessed the IGF axis at multiple time points across the intervention; all other trials took measurements at baseline and following the intervention.

3.1 Exercise Prescription Characteristics

The characteristics of exercise interventions are displayed in Table 1. Three studies utilised aerobic exercise (29, 31, 34), three used resistance exercise (30, 34, 35), one study used a combination of both aerobic and resistance exercise (33) and one study used a Tai Chi Chuan exercise protocol (32). Only one trial (34) compared two types of exercise prescription on the IGF axis. Duration of the interventions ranged from 12-26 weeks, with the frequency of prescribed sessions ranging from 2-5 sessions per week. Intensity of exercise varied according to the mode, however aerobic exercise was predominantly of moderate intensity, and was quantified according to heart rate, power outputs equivalent to oxygen consumption (VO2) thresholds and ratings of perceived exertion. Studies employing resistance-training protocols (30, 34, 35) progressively altered the prescription of sets, repetitions or intensity throughout the intervention. Resistance training prescription ranged from 2-4 sets at an intensity of 6-12 repetition maximum (RM), which was considered to be of moderate to high
intensity. One intervention (33) prescribed a specific dose of weekly physical activity, however specifications for frequency, duration or intensity of exercise were not provided.

3.2 Effects of Exercise Prescription on the IGF axis

The effects of exercise interventions on IGF-1 and IGF-2 are displayed in Table 2, and IGFBP-1, IGFBP-2 and IGFBP-3 in Table 3. IGF-1 was measured in all studies, with decreases (29, 31, 34), increases (33) and non-significant changes reported (30, 32, 35). In response to similar aerobic exercise interventions in breast cancer survivors, two studies (29, 31) demonstrated a significant decrease in IGF-1 of 7.3% (p=0.045) and 2.9% (p=0.026) from baseline, respectively. One study (34) found that 13 weeks of resistance training significantly reduced serum IGF-1 by 13.1% (p≤0.05) in prostate cancer patients with no further significant changes after an additional 13 weeks of training. No within-group changes in IGF-1 were observed in response to the parallel aerobic training group (p>.05). A significant increase (17.8%, p=0.007) in IGF-1 was observed in a group of colorectal cancer survivors following a home-based exercise protocol of combined aerobic and resistance exercise (33). No other significant changes in IGF-1 were observed in the remaining studies (30, 32, 35).

One study (35) reported a significant decrease in plasma IGF-2 (3.0%, p=0.02) in response to 26 weeks of progressive resistance training. A second study (29) reported similar decreases (2.4%) in IGF-2 in response to aerobic exercise however this was not statistically significant (p=0.101).

The most frequently measured binding protein, IGFBP-3, was reported to both increase (29, 33, 34), decrease (31, 34) and remain unchanged (32, 35) in response to exercise training. A significant 4.8% increase in IGFBP-3 (p=0.021) was reported in response to an aerobic exercise intervention in breast cancer survivors (29). Conversely, in response to a similar aerobic intervention in breast cancer survivors, a significant 4.1% decrease (p=0.006) was observed compared to the control group (31). Baseline IGFBP-3 levels were substantially
different among trials, ranging from 2160.8 ng.ml⁻¹ (29) to 4150.0 ng.ml⁻¹ (31). A significant 30.3% within-group increase (p=0.013) in response to a home-based resistance and aerobic exercise program was observed in colorectal cancer survivors (33). In the group of prostate cancer patients completing six months of either home-based aerobic or resistance exercise program, a significant 12.1% (p≤0.05) within-group increase in serum IGFBP-3 was observed in response to resistance training and a 23.7% (p≤0.05) within-group decrease in response to aerobic training (34). No significant changes in IGFBP-3 were reported in the remaining trials (32, 35). Reported IGFBP-3 values in one study (32) were approximately one hundred fold lower than all other trials, the reason for which is not clear.

No significant changes in IGFBP-1 or IGFBP-2 were reported in response to aerobic, resistance or Tai Chi Chuan based exercise in breast cancer survivors (29, 32, 35). Additionally no significant (p=0.35) changes in IGFBP-1 were observed in colorectal cancer survivors (33).

With only seven papers meeting the inclusion criteria and the heterogeneity of results, there is currently insufficient evidence to categorically determine the effects of exercise, and, more specifically, exercise prescription on the IGF axis in populations with a history of cancer. Results from two trials conducted in breast cancer survivors showed a decrease in IGF-1 in response to exercise compared with the control groups (29, 31). Beyond these decreases however, the IGF-1 changes in other studies changes were remarkably heterogeneous with substantial variation in the magnitude and direction. This heterogeneity of findings extended to changes in IGFBP-3 with bidirectional responses reported following exercise interventions. Notwithstanding differences among intervention populations and exercise interventions, the current scope of literature does not allow for discrete conclusions to be made regarding the effects of exercise on systemic IGF-1 and IGFBP-3. Importantly however, these findings do not preclude a possible relationship, rather the disparity strongly indicates that the
relationship between the IGF axis and exercise may be non-linear and influenced by numerous factors; the complexities of which are discussed below.

4. Mechanistic insights and future perspectives regarding exercise and the IGF axis in oncology

4.1 Insights from non-oncological populations

Whilst IGF axis changes have been assessed in populations with a history of cancer, several other studies have investigated these responses in healthy populations. Studies of healthy populations have reported similar inconsistencies in IGF axis response to exercise to those found in the oncology literature (36, 37). No changes in IGF-1 or IGFBP-3 were observed in similar year-long aerobic exercise interventions by McTiernan et al. (38) (45 min; moderate intensity; 5 days/week) and Friedenreich et al. (39) (45min; 70-80% heart rate reserve; 5 days/week) compared to controls. Utilising a shorter duration intervention, Arikawa and colleagues (40) demonstrated a small increase in IGFBP-3 in response to an aerobic exercise intervention [30min; 80-85% maximum heart rate (HRmax); 5 days/week; 16 weeks] in young women, with no concurrent change in IGF-1, IGFBP-1, or IGFBP-2. In contrast, decreases in systemic IGF-1 levels have been reported in response to high volume aerobic training (60min; cycling at lactate threshold; 5 days/week; 6 weeks) (41). Collectively, studies investigating the effect of exercise training on systemic IGF axis levels in both healthy populations and populations with a history of cancer have demonstrated inconsistent or non-significant findings.

4.2 Mechanistic determinants of the exercise response

This review demonstrates a paucity of data and a remarkable heterogeneity when considering the response of the IGF axis to exercise. An important caveat and possible determining factor to explain the discrepancies in the IGF axis response to exercise is baseline concentrations of the IGF ligands. Orsatti et al. (42) and Nishida et al. (41) investigated the effects of resistance
and aerobic training protocols, respectively on the IGF axis, however in contrast to previous investigations, they provided exploratory analyses into the individual responses of IGF-1. Exercise-induced changes in systemic IGF-1 from baseline to endpoint (delta percentage values) were linearly correlated ($r=-0.62$ (42); $r=-0.77$ (41)) with resting pre-intervention IGF-1 levels, demonstrating that participants with elevated baseline IGF-1 experienced the greatest decrease in response to exercise whilst those with lower baseline levels of IGF-1 experienced increases in response to training. These findings present an intriguing hypothesis for the specific role of exercise in the optimisation of the systemic IGF axis and subsequently provide greater scope for the interpretation of the results of the current review. Exercise may facilitate increases in systemic IGF ligand availability during deficient states to an optimal level at which the anabolic potential of the systemic IGF axis is maximised (43). After this optimisation, the autocrine intramuscular IGF axis may become more important in facilitating exercise-induced adaptation with minimal systemic changes (44-46). Conversely, in states of IGF ligand over-abundance, exercise may act to reduce systemic IGF-1 levels. This holds particular importance when considering that it is the deregulation and overexpression of IGF-1 and IGF-2 that is associated with the development and progression of carcinomas. Decreasing IGF concentrations in states of systemic overabundance may effectively reduce IGF-1R mediated signalling which can subsequently improve cancer outcomes through ablation of this mitotic signalling pathway. With this physiologically plausible dichotomy of the IGF ligand responses in mind, it seems appropriate that in populations with a relatively normative expression of these proteins it may be expected that there would be no exercise-mediated changes, an idea briefly suggested by Schmitz and colleagues (35). Comparatively, in populations with either elevated or reduced expression of IGF ligands, responses to exercise may be substantially more dynamic.

A key determinant of this hypothesis regarding changes in IGF ligand concentrations in response to exercise is what constitutes ‘abnormal’ levels of the IGF ligands, which is predicated on understanding the factors that regulate the expression of these proteins. A
principle determinant of both resting IGF-1 and IGFBP-3 levels is age. Both IGF-1 and IGFBP-3 demonstrate a continual increase to a pubertal peak before a gradual decline with ageing (47, 48). Accounting for the population age is therefore critical to understanding the normative systemic expression of both IGF-1 and IGFBP-3, and when comparing between populations. In the current literature there was a significant range in the age of populations, with mean age ranging from 53-72 years. Future trials should endeavour to utilise populations of a homogeneous age to reduce variability in the IGF axis related to age, or comparing against age-standardised reference ranges. However, caution should be extended when comparing populations to previously published reference ranges as these are often dependent on the assay method used for analysis, with considerable inter-assay variation reported (49). In recognition of this inter-assay variation, an international consensus statement on the standardisation of IGF-1 quantification was developed, which recommended a common IGF-1 standard (02/254) for assay calibration (50). Future trials should ensure that measurements of IGF or any comparisons to reference ranges adhere to these recommendations to ensure accuracy and comparability of results. In the present review, all studies except one (32) used an enzyme linked immunosorbent assay (ELISA) method for IGF ligand and binding protein measurement. Reference ranges for measures of IGF-1 and IGFBP-3 derived from the ELISA method adhering to the consensus statement are currently only available for paediatric populations (51). One set of IGF-1 reference ranges published prior to this consensus statement by Andreassen and colleagues (52) utilising the ELISA method reported near identical standard curves when comparing the manufacturer provided standard with the 02/254 standard and offers an acceptable reference range for IGF-1 levels until more extensive data are published. When considering the IGF-1 levels of studies included in this review against this reference range, the decrease in IGF-1 reported in the trial by Irwin et al. (31) was from a baseline value 109.1% greater than the mean of the age- and gender-matched range. The values reported by Santa Mina et al. (34) were approximately 85% higher than the reference mean, however a significant decrease was only reported from baseline to midpoint in response to resistance training. Interestingly, the decrease reported by Fairey et al. (29) was
from an initial value approximately 33.2% below the mean for this age group suggesting that factors beyond baseline levels likely influenced the IGF-1 response.

Interpreting changes in IGFBP-3 with reference to the baseline values allows for some important observations. Specifically, increases in IGFBP-3 tended to be reported in groups with baseline values between 2000-3000 ng.ml\(^{-1}\) (29, 33) whereas those that reported decreases had baseline levels of greater than 4000 ng.ml\(^{-1}\) (31, 34). The influence of baseline values appears particularly evident in the results reported by Santa Mina et al. (34), who demonstrated an IGFBP-3 increase in response to resistance training and a decrease in response to aerobic training. Before concluding that differential effects exist between exercise modalities, it should be noted that baseline IGFBP-3 values in the aerobic group were significantly greater (28%) than those in the resistance-training group. This disparity may explain, at least in part, why these opposing changes were observed. In the absence of extensive reference ranges utilising the ELISA method, this method of interpretation should only be considered exploratory until further data are available.

IGF-1 levels have been positively correlated with measures of body mass index, and whilst at the population level this effect was not of sufficient clinical significance to warrant weight-standardised reference ranges (47), at the individual level this may be important when considering the IGF axis response to exercise. Synthesis of IGF-1 occurs in a range of extra-hepatic tissues such as skeletal muscle, bone, cartilage and adipose tissue (53, 54). Whilst the main contributor to systemic levels is hepatic production, changes in the volume of tissue producing IGF-1 in an autocrine fashion may also translate to systemic alterations. With exercise, systemic IGF-1 alterations resulting from autocrine production is primarily concerned with changes in tissues that are also exercise-responsive, such as skeletal myocytes and adipocytes. Increases in skeletal muscle IGF-1R density and activation in response to exercise should also be considered as a potential mechanism for reducing systemic levels of IGF-1. Skeletal muscle IGF-1R density and activation should be interpreted concomitantly.
with measures of muscle volume, as the surface area of IGF-1-permeable myocytes will strongly influence the relationship between exercise and systemic IGF ligand alterations. Whilst body fat (fat mass or body fat percentage) and muscle volume was reported in 71.4 and 42.9% of studies, respectively, only one study (35) utilised the more accurate dual energy x-ray absorptiometry method as compared with bioelectric impedance or skinfold measures (55). Given the potential influence of body composition on the relationship between the IGF axis and exercise, quantification of concurrent changes in these body composition parameters beyond basic anthropometric measures to include more accurate and reproducible measurements is recommended for future exercise interventions measuring the IGF axis.

Importantly, the potential non-linearity of the IGF axis response to exercise and its relationship to age and body mass may necessitate the inclusion of more individualised analytics in preference to strictly population- or group-based analysis. In several studies (29, 31-33, 35) there was substantial variance both within groups at baseline and in the magnitude of change in response to exercise for several IGF axis markers. Specifically, the baseline IGF-1 coefficients of variation in the exercise groups by Fairey et al. (29) and Lee et al. (33) were 43.2% and 44.5%, respectively. Furthermore, coefficients of variation of the mean changes in systemic IGF-1 levels in response to the interventions ranged from 75.9-218.4% in the four studies reporting this data (29, 31, 32, 35). Similar variances in the mean changes in IGFBP-3 in response to exercise were also reported (42.1-519.3%) (29, 31, 35). Collectively, these data suggest considerable individual IGF axis variation at baseline and in response to exercise, with important determinants of this response likely overlooked by population analysis. In addition to age and body mass, differences in time since diagnosis and treatment, as well as types of treatment may contribute to the observed variability. Mean time since diagnosis was only reported in three studies and ranged from 1.5-3.6 years (31, 33, 35). Average time since treatment was only reported in two studies (29, 35), ranging from 1.1-1.2 years. The majority of studies reported information relating to stage of disease (29, 31, 33-35) with some also explicitly specifying a range of stages (most commonly stage I to III) as part of the inclusion
criteria (29, 31-33). Irwin et al. (31) specifically analysed the effect of breast cancer stage on the IGF axis response. Whilst this factor did not modify the effect of exercise, accounting for stage of disease may provide additional insight when investigating the effects of exercise on the IGF axis. Whilst participants in the included investigations were not currently undergoing surgical, chemotherapeutic or radiation treatment, current hormone therapy use was prevalent amongst breast cancer survivors, with 46% (29), 81% (35) and 65% (31) of participants undergoing some form of hormone therapy reported in three of the four trials. All participants (100%) in the studies of men with prostate cancer were undergoing current androgen deprivation therapy for in situ carcinomas (30, 34). For clinically meaningful sub-analyses to occur according to these potential determinants of the variance observed in the IGF axis response to exercise, studies need to be of a sufficient sample size. In the present review, no studies reported sample size or power calculations, likely due to the predominance of pilot studies, however there was considerable variation in the sample size of the included investigations. The sample size of single-group intervention studies ranged from 10-17 participants (30, 33), whereas randomised controlled trials ranged from 19-85 participants (29, 31, 32, 34, 35). It is strongly recommended that future trials ensure that the sample sizes are sufficient to allow for sub-analyses to be performed, providing greater scope for understanding the relationship between the IGF axis substituents and various moderating factors. Given our developing understanding of the IGF axis response to exercise, the inconsistency and heterogeneity of current data makes it difficult to perform power calculations for informing sample sizes. In lieu of this, we recommend that study populations be drawn from a sample that minimises the variability associated with possible influencing factors of the IGF axis response, particularly stage of disease, time since diagnosis and treatment as well as types of treatment to enhance the homogeneity of the population. We also recommend that these data be more consistently reported. Inclusion of meaningful sub-analyses in future well powered trials may enable detection of more subtle relationships between exercise and the IGF axis in this population and add greater scope for understanding the inconsistency of current results.
4.3 Differential physiological roles of the IGF axis in response to exercise

A limitation of oncological research investigating the IGF axis in response to exercise is the exclusive focus on carcinogenic properties of the systemic IGF ligands (54, 56). Within the scope of characterising the effect of exercise on the IGF axis, it is critical to recognise the non-carcinogenic, anabolic roles of the IGF axis in exercise-responsive tissues within the body. This is particularly important as the extrapolation of this understanding is integral to the physiological basis by which exercise may influence the systemic IGF axis. Similar to the carcinogenic potential of the IGF axis mediated through IGF-1R activation, the anabolic potential of the IGF axis is ascribed to the activation of this receptor in myocytes to promote cellular proliferation and growth (57). A point of contention is the relative contribution of systemic as compared with autocrine IGF-1 in initiating these anabolic processes and how these processes are influenced by exercise. In vivo murine models have provided key insights into the isolated importance of systemic and local muscular IGF-1 expression in facilitating anabolic adaptations to exercise. In a liver-specific IGF-1 deficient murine model (expressing 70% reductions in systemic IGF-1 compared to wild type models), serological IGF-1 deficiency did not impair improvements in muscular performance in response to exercise training (58), whereas intra-muscular overexpression of local IGF-1 accelerated muscular regeneration after a period of immobilisation-induced atrophy in IGF-1 normative mice (59).

In clinical populations characterised by cachexia and muscular atrophy, local IGF-1 has been shown to mediate the anabolic response of skeletal muscle to exercise (60-62). Hambrecht and colleagues (60) demonstrated local muscular IGF-1 increased by 81% with no parallel change in systemic IGF-1 in response to six months of aerobic exercise training [20 min/day; 70% maximal oxygen uptake (VO2max)]. Utilising a progressive resistance-training program (3x8 reps; 80% 1RM; 2 days/week; 24 weeks), Lemmey et al. (61) found significant increases in total lean and appendicular muscle mass in older adults with rheumatoid arthritis. These changes were associated with 41% and 73% increases in muscular IGF-1 and IGFBP-3,
respectively, whereas no changes in systemic IGF-1, IGF-2, IGFBP-1 or IGFBP-3 were observed.

To further explore this relationship, it must be noted that IGF-1 is expressed in three specific isoforms: IGF-1Ea, IGF-1Eb and IGF-1Ec. IGF-1Ea and IGF-1Eb are splice variants typically found in systemic circulation (primarily of hepatic origin) whereas the IGF-1Ec is an autocrine variant exclusively produced locally in myocytes. IGF-1Ec is up regulated in response to mechanical stimuli (e.g. exercise) leading to this isoform being termed mechano-growth factor (MGF) (43). In younger men (29.5±1.5 years), Hameed et al. (63) demonstrated acute increases in MGF in response to high-resistance knee extension (10x6 repetitions; 80% 1RM) with no changes in IGF-1Ea. Ahtiainen et al. (64) reported acute increases in both MGF and IGF-1Ea in response to heavy-resistance exercise (5x10RM leg press and 4x10RM squats). Conversely Popov et al. (65) found that only a high intensity stimulus (75% 1RM) was sufficient to acutely increase MGF levels, with no changes observed in response to a moderate intensity [50% 1RM] and no changes in IGF-1Ea reported in either condition.

Whilst further research is required to determine the contribution of the IGF axis to anabolic adaptation, it is generally thought that improvements are mediated through local rather than systemic expression (36, 66) with MGF the primary regulator of these processes in response to exercise (43, 67, 68). Furthermore, local myocyte expression of the IGF-1R has been shown to increase in response to acute resistance exercise (69, 70). Wilborn and colleagues (71) demonstrated an identical increase in the expression of muscular IGF-1R mRNA in response to both higher intensity (80%-85% 1RM) and lower intensity (60-65% 1RM) resistance training, peaking two hours post-exercise and returning to baseline after six hours.

In the same cohort, Taylor et al. (72) demonstrated elevated IGF-1R phosphorylation up to six hours post-exercise in skeletal muscle. It has been reported that during exercise, active skeletal muscle surpasses the liver as the principle producer of systemic IGF-1 (autocrine production) and also is the principle extractor of IGF-1 from circulation (43, 67). Increases in the expression and activation of the IGF-1R may potentiate a transient post-exercise period of
increased IGF ligand permeability and subsequent cellular signalling. This increase in receptor density and activation suggests a plausible biological mechanism by which acute and chronic exercise training can decrease systemic levels of the IGF ligands through increased myocyte uptake. In response to exercise there appears to be a physiological capacity for both increases and decreases in systemic levels of IGF ligands, however the determinants of this direction remain to be confirmed which reflects the current inconsistency of results. The local and systemic expression of the IGF axis appears inextricably related within the context of exercise. Quantification of intramuscular expression of the ligands, binding proteins or receptors of the IGF axis was not included in any of the trials within the current review, limiting conclusions pertaining to the effects of exercise prescription. Future trials should endeavour to quantify the intramuscular expression of the IGF axis constituents in response to exercise concurrently with systemic changes to determine the exercise-induced response and any differential effects between systems (see the analysis of Lemmey et al. (61) for reference).

5. Conclusions and summary of future directions

This review has several limitations worthy of mention. Firstly, analysis was only completed on published results; relevant unpublished data may have been omitted. Secondly, this review has focussed on the chronic systemic IGF axis response and has not considered the acute response to exercise. To the best of our knowledge, only one trial to date has investigated the acute response of IGF-1 to exercise in cancer survivors (30). This remains an important area of future research when investigating the effects of exercise on the IGF axis in cancer survivors.

This review has revealed inconsistency in the response of the systemic IGF axis to exercise in populations with a history of cancer. The available literature does not allow for discrete conclusions to be made regarding the effects of specific exercise prescription, reflecting the
need for continued development of this area to enhance our understanding of the IGF axis response to exercise. Whilst the pathophysiological role of the IGF axis in tumour proliferation is well supported (54, 73), the potential mediatory role of exercise therapy on this series of proteins remains unclear. Furthermore, it is worth noting the distinction between expression of the IGF axis in populations with current malignancy or post-malignancy. The majority of studies included in the present review investigated survivorship (post-malignancy) populations, in which the clinical focus regarding the tumorigenic properties of the systemic IGF axis relates to reducing the risk of cancer recurrence in potentially malignant tissue. In comparison to survivorship populations, there appears to be substantial differences in the IGF axis with current malignancy, with both the systemic and tissue expression of these factors to be considered. In malignant tissue, the IGF-1R is often overexpressed in a number of cancers (74, 75), with the degree of overexpression being correlated with tumour stage in some colorectal cancers (76, 77). When considering the systemic IGF axis, some studies have also reported elevated levels of systemic IGF ligands in patients with current breast (78), prostate (79) or colorectal (80-82) cancers, however others have reported conflicting results (83, 84). Cancerous tumours are capable of producing IGF ligands in an autocrine or paracrine manner (85), however the extent to which this influences systemic levels remains to be confirmed. Given the potential relationship between baseline levels of the IGF ligands and the exercise response, future exercise trials in populations with current malignancy are warranted to better understand the effects of exercise on the systemic IGF axis and subsequent IGF-1R signalling.

Although the development of IGF-1R inhibitory therapies is promising, these therapies need to include targeted cellular delivery or delivery at concentrations so as to avoid systemic toxicity that would adversely affect adaptive IGF-1R signalling in selective tissues (54, 86). Alternative strategies include using monoclonal antibodies to reduce the bioavailability of ligands capable of initiating IGF-1R signalling (73). To this end, exercise may be an effective targeted therapy by way of its physiological potential to reduce systemic IGF ligands capable
of IGF-1R activation in conditions of overabundance without adversely affecting the anabolic role of this signalling in skeletal myocytes. Additionally, IGF-1R inhibitors have been suggested to be more effective treatments in cancers with select genotypes and phenotypes such as in KRAS-mutant (rather than wild type) colorectal or lung cancers and triple negative (rather than hormone receptor positive) breast cancers (73, 86). Future exercise trials assessing tumour specific outcomes related to the IGF-1R and its intracellular signalling pathways may also benefit from the inclusion of this type of distinction. Given the importance of the IGF system in oncology, future research is needed to enhance our understanding of the response of the systemic IGF axis to exercise. To achieve this, future trials should employ a more expansive analysis of the IGF axis to include both its differential roles in systemic and local tissues. Additionally, the effect of key determinants of the IGF axis needs to be considered to better understand and predict the responses to exercise at both the population and individual levels. Future trials addressing these aspects will improve our ability to determine the role of exercise as an adjunctive oncological treatment.
References

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### Table 1: Study Characteristics

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Type</th>
<th>Population [Age (years), body mass (kg), BMI (kg.m⁻²) = mean (SD)]</th>
<th>Exercise Prescription</th>
<th>Frequency</th>
<th>Protocol and Outcomes [I: Intervention; C: Control]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fairey et al., 2003 (29)</td>
<td>RCT</td>
<td>T: breast cancer; n = 53; age = [I] 59.0 (5.0) [C] 58.0 (6.0); body mass = [I] 78.1 (20.4) [C] 79.4 (16.4); BMI = [I] 29.4 (7.4) [C] 29.1 (6.1)</td>
<td>A</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Schmitz et al., 2005 (35)</td>
<td>RCT</td>
<td>T: breast cancer; n = 85; age = [I] 53.3 (8.7) [C] 52.8 (7.6); body mass = [I] 69.2 (2.2) [C] 69.0 (2.2); BMI = [I] 25.9 (0.7) [C] 25.8 (0.7)</td>
<td>R</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Irwin et al., 2009 (31)</td>
<td>RCT</td>
<td>T: breast cancer; n = 75; age = [I] 56.4 (9.5) [C] 55.6 (7.7); body mass = [I] 81.0 (16.8) [C] 79.3 (21.3); BMI = [I] 30.4 (6.0) [C] 30.1 (7.4)</td>
<td>A</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>Galvao et al., 2008 (30)</td>
<td>SGI</td>
<td>T: prostate cancer; n = 10; age = 70.3 (8.3)</td>
<td>R</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Janelins et al., 2011 (32)</td>
<td>RCT</td>
<td>T: breast cancer; n = 19; age = [I] 54.3 (10.6) [C] 52.7 (6.7); body mass = [I] 66.7 (14.9) [C] 66.7 (9.8); BMI = [I] 24.9 (5.8) [C] 25.0 (4.4)</td>
<td>TC</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Lee et al., 2013 (33)</td>
<td>SGI</td>
<td>T: colorectal cancer; n = 17 (7 women); age = 55.1 (13.7); body mass = 61.3 (10.6); BMI = 23.1 (3.4)</td>
<td>A and R</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Santa Mina et al., 2013 (34)</td>
<td>RCT</td>
<td>T: prostate cancer; n = 26; age = [A] 70.6 (8.1) [R] 73.6 (8.8); body mass = [A] 86.2 (9.9) [R] 80.3 (13.2); BMI = [A] 28.5 (3.3) [R] 27.4 (5.0)</td>
<td>A or R</td>
<td>26</td>
<td>5</td>
</tr>
</tbody>
</table>

*Only RCT component of the study by Schmitz et al. (35) is included in the analysis.*

A: aerobic exercise group; BML: body mass index; C: control group; ELISA: enzyme linked immunosorbent assay; HR: heart rate; HRR: heart rate reserve I: intervention group; IGF: insulin-like growth factor; IGFBP: insulin-like growth factor binding protein; IRMA: immunoradiometric assay; kg: kilogram; MET: metabolic equivalent; n: number; NR: not reported; R: resistance training group; Reps: repetitions; RCT: randomised controlled trial; RM: repetition maximum; SD: standard deviation; SE: standard error; SGI: single group intervention study; T = cancer type; TC: Tai Chi Chuan; VO₂: volume of oxygen consumed; 1RM: one repetition maximum.
Table 2: Effects of exercise interventions on IGF-1 and IGF-2

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Baseline [1] [Mean (SD)]</th>
<th>1st Endpoint [2] [Mean (SD)]</th>
<th>2nd Endpoint [3] [Mean (SD)]</th>
<th>Within group analysis</th>
<th>Between groups analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean change [Mean (SD)]</td>
<td>Δ percentage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIG-1 (ng.ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Fairey et al., 2003 (29)</td>
<td>I: 67.4 (29.1)</td>
<td>62.5 (23.9)</td>
<td>NA</td>
<td>-4.9 (10.7)</td>
<td>-7.3%</td>
</tr>
<tr>
<td></td>
<td>C: 70.0 (21.5)</td>
<td>72.6 (24.8)</td>
<td>NA</td>
<td>2.5 (14.8)</td>
<td>3.6%</td>
</tr>
<tr>
<td>2 Schmitz et al., 2005 (35)</td>
<td>I: 172.9 (11.6)</td>
<td>181.2 (11.6)</td>
<td>NA</td>
<td>8.3 (6.3)</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td>C: 194.3 (11.4)</td>
<td>190.3 (11.4)</td>
<td>NA</td>
<td>-4.0 (6.1)</td>
<td>-2.0%</td>
</tr>
<tr>
<td>3 Irwin et al., 2009 (31)</td>
<td>I: 213.3 (12.6)</td>
<td>207.1 (11.2)</td>
<td>NA</td>
<td>-7.4 (6.0)</td>
<td>-2.9%</td>
</tr>
<tr>
<td></td>
<td>C: 232.3 (18.7)</td>
<td>243.7 (18.5)</td>
<td>NA</td>
<td>12.7 (6.4)</td>
<td>4.8%</td>
</tr>
<tr>
<td>4 Galvao et al., 2008 (30)</td>
<td>I: 158.9 (19.4)</td>
<td>161.4 (16.1)</td>
<td>156.3 (14.3)</td>
<td>NA</td>
<td>[1-2] 1.6%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5 Janelins et al., 2011 (32)</td>
<td>I: 156.8 (19.6)</td>
<td>129.5 (43.8)</td>
<td>NA</td>
<td>-27.3 (45.1)</td>
<td>-17.4%</td>
</tr>
<tr>
<td></td>
<td>C: 111.8 (82.6)</td>
<td>95.1 (58.7)</td>
<td>NA</td>
<td>-16.6 (66.5)</td>
<td>-14.9%</td>
</tr>
<tr>
<td>6 Lee et al., 2013 (33)</td>
<td>I: 135.4 (60.2)</td>
<td>159.5 (62.1)</td>
<td>NA</td>
<td>17.8%</td>
<td>NA</td>
</tr>
<tr>
<td>7 Santa Mina et al., 2013 (34)</td>
<td>I (A): 159.6 (55.2)</td>
<td>169.7 (67.5)</td>
<td>161.9 (45.9)</td>
<td>NA</td>
<td>[1-2] 6.3%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (R): 159.1 (51.2)</td>
<td>138.3 (42.6)</td>
<td>146.4 (49.5)</td>
<td>NA</td>
<td>[1-2] -13.1%</td>
<td>[1-3] -8.0%</td>
</tr>
</tbody>
</table>

IGF-2 (ng.ml⁻¹)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Baseline [1] [Mean (SD)]</th>
<th>1st Endpoint [2] [Mean (SD)]</th>
<th>2nd Endpoint [3] [Mean (SD)]</th>
<th>Within group analysis</th>
<th>Between groups analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean change [Mean (SD)]</td>
<td>Δ percentage</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 Fairey et al., 2003 (29)</td>
<td>I: 824.9 (155.5)</td>
<td>805.0 (139.9)</td>
<td>NA</td>
<td>-19.9 (97.1)</td>
<td>-2.4%</td>
</tr>
<tr>
<td></td>
<td>C: 714.5 (148.9)</td>
<td>735.3 (152.4)</td>
<td>NA</td>
<td>20.9 (80.5)</td>
<td>2.9%</td>
</tr>
<tr>
<td>2 Schmitz et al., 2005 (35)</td>
<td>I: 898.0 (34.9)</td>
<td>871.8 (34.9)</td>
<td>NA</td>
<td>-26.2 (16.7)</td>
<td>-3.0%</td>
</tr>
<tr>
<td></td>
<td>C: 891.3 (34.4)</td>
<td>919.5 (34.4)</td>
<td>NA</td>
<td>28.3 (16.3)</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

a Only RCT component of the study by Schmitz et al. (35) is included in the analysis
b Data presented as mean (SE)
A: aerobic exercise group; C: control group; I: intervention group; IGF: insulin-like growth factor; NA: not applicable; R: resistance training group; SD: standard deviation; SE: standard error
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Baseline [1] [Mean (SD)]</th>
<th>1st Endpoint [2] [Mean (SD)]</th>
<th>2nd Endpoint [3] [Mean (SD)]</th>
<th>Within group analysis</th>
<th>Between groups analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean change</td>
<td>Δ percentage p value p value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[Mean (SD)]</td>
<td>NA</td>
</tr>
<tr>
<td>IGFBP-1 (ng.ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Fairey et al., 2003 (29)</td>
<td>I: 47.5 (32.3) C: 48.2 (29.8)</td>
<td>53.2 (30.4)</td>
<td>NA</td>
<td>5.6 (13.4)</td>
<td>12.0% NA p = 0.774</td>
</tr>
<tr>
<td></td>
<td>I: 52.4 (34.2) C: 37.8 (28.8)</td>
<td>52.4 (34.2)</td>
<td>NA</td>
<td>4.2 (21.2)</td>
<td>8.7% NA</td>
</tr>
<tr>
<td>2 Schmitz et al., 2005 (35)</td>
<td>I: 36.9 (2.9) C: 36.9 (2.8)</td>
<td>34.7 (2.9)</td>
<td>NA</td>
<td>-2.1 (2.3)</td>
<td>-5.8% NA p = 0.36</td>
</tr>
<tr>
<td></td>
<td>I: 37.8 (2.8) C: 37.8 (2.8)</td>
<td>37.8 (2.8)</td>
<td>NA</td>
<td>0.8 (2.3)</td>
<td>2.2% NA</td>
</tr>
<tr>
<td>3 Janelsins et al., 2011 (32)</td>
<td>I: 72.6 (25.6) C: 92.2 (39.0)</td>
<td>76.4 (42.8)</td>
<td>NA</td>
<td>3.8 (27.3)</td>
<td>5.2% NA p &gt; 0.05</td>
</tr>
<tr>
<td></td>
<td>I: 101.3 (50.0) C: 101.3 (50.0)</td>
<td>101.3 (50.0)</td>
<td>NA</td>
<td>9.1 (36.4)</td>
<td>9.9% NA</td>
</tr>
<tr>
<td>4 Lee et al., 2013 (33)</td>
<td>I: 6.2 (5.1)</td>
<td>7.3 (6.3)</td>
<td>NA</td>
<td>NA</td>
<td>17.0% p = 0.35</td>
</tr>
<tr>
<td>IGFBP-2 (ng.ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Schmitz et al., 2005 (35)</td>
<td>I: 421.7 (29.5) C: 472.9 (29.0)</td>
<td>449.6 (29.4)</td>
<td>NA</td>
<td>27.9 (16.8)</td>
<td>6.6% NA p = 0.30</td>
</tr>
<tr>
<td></td>
<td>I: 476.5 (29.1) C: 476.5 (29.1)</td>
<td>476.5 (29.1)</td>
<td>NA</td>
<td>3.6 (16.4)</td>
<td>0.8% NA</td>
</tr>
<tr>
<td>IGFBP-3 (ng.ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Fairey et al., 2003 (29)</td>
<td>I: 2160.8 (421.1) C: 2146.2 (438.2)</td>
<td>2264.2 (435.4)</td>
<td>NA</td>
<td>103.4 (224.7)</td>
<td>4.8% NA p = 0.021</td>
</tr>
<tr>
<td></td>
<td>I: 2069.1 (478.4) C: 2069.1 (478.4)</td>
<td>2069.1 (478.4)</td>
<td>NA</td>
<td>-77.1 (313.5)</td>
<td>-3.6 NA</td>
</tr>
<tr>
<td>2 Schmitz et al., 2005 (35)</td>
<td>I: 4339.7 (133.2) C: 4519.7 (130.9)</td>
<td>4356.2 (132.7)</td>
<td>NA</td>
<td>16.5 (85.9)</td>
<td>0.4% NA p = 0.32</td>
</tr>
<tr>
<td></td>
<td>I: 4356.2 (132.7) C: 4356.2 (132.7)</td>
<td>4356.2 (132.7)</td>
<td>NA</td>
<td>135.3 (83.8)</td>
<td>3.0% NA</td>
</tr>
<tr>
<td>3 Irwin et al., 2009 (31)</td>
<td>I: 4150.0 (160.0) C: 4480.0 (170.0)</td>
<td>3980.0 (160.0)</td>
<td>NA</td>
<td>-190.0 (80.0)</td>
<td>-4.1% NA p = 0.006</td>
</tr>
<tr>
<td></td>
<td>I: 4610.0 (180.0) C: 4610.0 (180.0)</td>
<td>4610.0 (180.0)</td>
<td>NA</td>
<td>150.0 (100.0)</td>
<td>2.9% NA</td>
</tr>
<tr>
<td>4 Janelsins et al., 2011 (32)</td>
<td>I: 39.2 (6.3) C: 40.8 (13.6)</td>
<td>40.1 (7.3)</td>
<td>NA</td>
<td>0.9 (3.1)</td>
<td>2.3% NA p &gt; 0.05</td>
</tr>
<tr>
<td></td>
<td>I: 40.1 (15.1) C: 40.1 (15.1)</td>
<td>40.1 (15.1)</td>
<td>NA</td>
<td>-0.7 (3.8)</td>
<td>-1.7% NA</td>
</tr>
<tr>
<td>5 Lee et al., 2013 (33)</td>
<td>I: 2670.0 (1480.0)</td>
<td>3480.0 (1000.0)</td>
<td>NA</td>
<td>NA</td>
<td>30.3% p = 0.013</td>
</tr>
<tr>
<td>6 Santa Mina et al., 2013 (34)</td>
<td>I (A): 5582.7 (1514.3)</td>
<td>4770.4 (2579.1)</td>
<td>NA</td>
<td>4259.8 (1349.2)</td>
<td>[1-2] -14.6%</td>
</tr>
<tr>
<td></td>
<td>I (B): 4360.5 (1370.9)</td>
<td>4321.3 (1205.5)</td>
<td>NA</td>
<td>4887.9 (1639.7)</td>
<td>NA</td>
</tr>
</tbody>
</table>

| a Only RCT component of the study by Schmitz et al. (35) is included in the analysis |
| b Data presented as mean (SE) |
| A: aerobic exercise group; C: control group; I: intervention group; IGFBP: insulin-like growth factor binding protein; NA: not applicable; R: resistance training group; SD: standard deviation; SE: standard error |
Figure Legend

Figure 1. Consort diagram illustrating the search process.
Figure 1.
The influence of exercise on the insulin-like growth factor axis in oncology: physiological basis, current and future perspectives

James L Devin, Kate A Bolam, David G Jenkins, et al.

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