The Influence of Exercise on the Insulin-like Growth Factor Axis in Oncology: Physiological Basis, Current, and Future Perspectives

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Abstract

Exercise and physical activity have been shown to reduce the risk of many common cancers and strongly influence tumor biology. A cause–effect mechanism explaining this relationship is dependent on cellular pathways that can influence tumor growth and are exercise responsive. The insulin-like growth factor (IGF) axis is reported to promote the development and progression of carcinomas through cellular signaling in cancerous tissues. This review summarizes the physiologic 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.

Physiologic Basis of the Insulin-like Growth Factor Axis in Oncology

The weight of epidemiologic 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 physiologic review of the IGF axis is beyond the scope of this review; those interested are referred to the work of Annunziata and colleagues (10). Briefly, the IGF axis consists of two specific ligands, (i) IGF1 and (ii) IGF2, which interact with their primary cell-surface tyrosine kinase receptor, the IGF1 receptor (IGF1R). Activation of the IGF1R by IGF1 or IGF2 is achieved through ligands IGF1 and IGF2 initiates cellular signaling through the MAPK and PI3K pathways, which facilitates DNA synthesis, cellular survival, proliferation, and differentiation in the target cell (8, 12). Although these processes of cellular signaling and receptor activation are central to the development and growth of many tissues (13), activation of the IGF1R and subsequent signaling in cancerous cells is thought to promote tumorigenesis and progression (14). The strength of association between IGF1 signaling and carcinogenesis is such that pharmacologic methods of IGF1R signaling ablation are being actively pursued through preclinical and clinical trials as potential cancer treatments (14, 15).

In circulation, the degree of IGF1R activation in cancerous tissues is dependent on systemic levels of the IGF ligands. Indeed metaanalytical data show that elevated levels of systemic IGF1 are associated with an increase in colorectal (16), prostate (17, 18) and premenopausal breast cancer (18) risk. Although the epidemiologic evidence is inconsistent, several preclinical in-vitro (19–22) and in-vivo (23, 24) tumor models have strengthened the causal relationship between elevated IGF1 concentrations and increased tumor growth and development. The bioactivity and subsequent mitogenicity of the IGF ligands in cancerous cells are modulated by a number of high-affinity IGF-binding proteins (IGFBP1 to IGFBP6). IGFBPs competitively bind to IGF1 and IGF2, reducing the capability of these ligands to bind with their cognate receptors (25). Although IGFBPs are thought to generally inhibit the actions of the IGF ligands as a result of this competitive binding, the IGFBPs also exhibit IGF1R 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 tumor microenvironment enhancing delivery of the IGF ligands to the IGF1R (11, 26).

Reducing IGF1R signaling in carcinogenic tissues is an important focus within the oncology field. Exercise training is hypothesized to elicit physiologic changes in systemic IGF ligand and binding protein bioavailability, which may indirectly influence IGF1R signaling. 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 IGF1R inhibition underlines the need for further exploration of the IGF axis. Furthermore, the complex nature of the IGF axis response to exercise, including the capacity for the IGF axis to modulate in response to exercise stress, necessitates a specific and in-depth analysis of both the physiology of this relationship and the determining factors that can maximize the anticarcinogenic effect of exercise.

The purpose of this review was to summarize 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 physiologic basis and mechanisms underpinning the relationship between exercise and the IGF axis on carcinogenic progression.

Search Strategy

To define the current literature, searches were conducted in August 2014 utilizing 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, and control*) and (population: adult*, human*, and subjects) and (intervention: exercise*, training, weight*, resistance*, aerobic*, strength*, muscular*, endurance, walk*, running, and cycling) and (primary outcome: insulin* like* growth* factor*, IGF* and IGF-binding protein*). The inclusion criteria were (i) design: randomized controlled trials, controlled trials, and single-group intervention studies; (ii) population: men and/or women aged $\geq 18$ years old, previously diagnosed with cancer but not currently undergoing any form of surgery, chemotherapy, or radiotherapy; (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); and (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.

Current Scope of the IGF Axis Response to Exercise in Oncology

The results of the search process are detailed in Fig. 1. A total of 4,251 articles were retrieved from database searching ($n = 4,250$) 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 randomized 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 IGF1, with all but one (30) also measuring its principle binding protein IGFBP3. Four of the seven studies also assessed additional components of the IGF axis with IGFBP2 measured in two studies (29, 35), IGFBP1 measured in four studies (29, 32, 33, 35), and IGFBP2 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.

Exercise prescription characteristics

The characteristics of exercise interventions are displayed in Table 1. Three studies utilized 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 to 26 weeks, with the frequency of prescribed sessions ranging from 2 to 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 ($\text{VO}_2$) thresholds, and ratings of perceived exertion. Studies using resistance-training protocols (30, 34, 35) progressively altered the prescription of sets, repetitions, or intensity throughout the intervention. Resistance training prescription ranged from 2 to 4 sets at an intensity of 6 to 12 repetition maximum (RM), which was considered to be of moderate to...
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>Duration (weeks)</th>
<th>Frequency (sessions/week)</th>
<th>Exercise prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 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>2 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>3 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>4 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>5 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>6 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>7 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>

Abbreviations: A, aerobic exercise group; BMI, body mass index; C, control group; HR, heart rate; HRR, heart rate reserve; I, intervention group; IRMA, immunoradiometric assay; kg, kilogram; MET, metabolic equivalent; n, number; NR, not reported; R, resistance training group; Reps, repetitions; RCT, randomized controlled trial; SGI, single-group intervention study; T, cancer type; TC, Tai Chi Chuan; VO2, volume of oxygen consumed; RM, repetition maximum.

*Only RCT component of the study by Schmitz et al. (35) is included in the analysis.
Abbreviations: A, aerobic exercise group; C, control group; I, intervention group; NA, not applicable; R, resistance training group.

Effects of exercise interventions on IGF1 and IGF2

Table 2. Effects of exercise interventions on IGF1 and IGF2

<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>IGF1 (ng.mL(^{-1}))</td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>1 Fairey et al., 2003 (29)</td>
<td>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>2 Schnitz et al., 2005 (35)</td>
<td>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>3 Irwin et al., 2009 (31)</td>
<td>233.3 (12.2)</td>
<td>207.1 (11.2)</td>
<td>NA</td>
<td>−7.4 (6.0)</td>
<td>−2.9%</td>
</tr>
<tr>
<td>4 Galvao et al., 2008 (30)</td>
<td>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>5 Janelins et al., 2011 (32)</td>
<td>158.6 (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>6 Lee et al., 2013 (33)</td>
<td>135.4 (60.2)</td>
<td>159.5 (62.1)</td>
<td>NA</td>
<td>−16.6 (66.5)</td>
<td>−14.9%</td>
</tr>
<tr>
<td>7 Santa Mina et al., 2013 (34)</td>
<td>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>
<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) −1.3%</td>
</tr>
<tr>
<td>IGF2 (ng.mL(^{-1}))</td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>1 Fairey et al., 2003 (29)</td>
<td>824.9 (155.9)</td>
<td>805.0 (139.9)</td>
<td>NA</td>
<td>−19.9 (97.1)</td>
<td>−2.4%</td>
</tr>
<tr>
<td>2 Schnitz et al., 2005 (35)</td>
<td>743.5 (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>3 Fairey et al., 2013 (33)</td>
<td>898.0 (34.9)</td>
<td>878.3 (34.9)</td>
<td>NA</td>
<td>−26.2 (16.7)</td>
<td>−3.0%</td>
</tr>
<tr>
<td>4 Galvao et al., 2008 (30)</td>
<td>893.4 (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>

Abbreviations: A, aerobic exercise group; C, control group; I, intervention group; NA, not applicable; R, resistance training group.

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

Data presented as mean (SE).

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.

Effects of exercise prescription on the IGF axis

The effects of exercise interventions on IGF1 and IGF2 are displayed in Table 2, and IGFBP1, IGFBP2, and IGFBP3 in Table 3. IGF1 was measured in all studies, with decreases (29, 31, 34), increases (33), and nonsignificant 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 IGF1 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 IGF1 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 IGFB1 were observed in response to the parallel aerobic training group (P > 0.05). A significant increase (17.8%; P = 0.007) in IGFB1 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 IGFB1 were observed in the remaining studies (30, 32, 35).

One study (35) reported a significant decrease in plasma IGF2 (3.0%; P = 0.02) in response to 26 weeks of progressive resistance training. Another study (29) reported similar decreases (2.4%) in IGF2 in response to aerobic exercise; however, this was not statistically significant (P = 0.101).

The most frequently measured binding protein, IGFBP3, 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 IGFBP3 (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 with the control group (31). Baseline IGFBP3 levels were substantially different among trials, ranging from 2,160.8 ng.mL\(^{-1}\) (29) to 4,150.0 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 6 months of either home-based aerobic or resistance exercise program, a significant 4.1% decrease (P = 0.05) within-group increase in serum IGFBP3 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 IGFBP3 were reported in the remaining trials (32, 35). Reported IGFBP3 values in one study (32) were approximately 100-fold lower than all other trials, the reason for which is not clear.

No significant changes in IGFBP1 or IGFBP2 were reported in response to aerobic, resistance, or Tai Chi Chuan–based exercise in breast cancer survivors (29, 32, 35). In addition no significant (P = 0.35) changes in IGFBP1 were observed in colorectal cancer survivors (33).

With only seven articles 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 IGF1 in response to exercise compared with the control groups (29, 31). Beyond these decreases however, the IGF1 changes in other studies changes...
Mechanistic Insights and Future Perspectives Regarding Exercise and the IGF Axis in Oncology

Insights from nononcological populations

Although 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 IGFI or IGFBP3 were observed in similar year-long aerobic exercise interventions by McTiernan and colleagues (ref. 38; 45 minutes; moderate intensity; 5 days/week) and Friedenreich and colleagues (ref. 39; 45 minutes; 70%–80% heart rate reserve; 5 days/week) compared with controls. Utilizing a shorter-duration intervention, Arikawa and colleagues (40) demonstrated a small increase in IGFBP3 in response to an aerobic exercise intervention [30 minutes; 80%–85% maximum heart rate (HRmax); 5 days/week; 6 weeks] in young women, with no concurrent change in IGFI, IGFBP1, or IGFBP2. In contrast, decreases in systemic IGFI levels have been reported in response to high volume aerobic training (60 minutes; cycling at lactate threshold; 5 days/week; 6 weeks; ref. 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 nonsignificant findings.

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 and colleagues (42) and Nishida and colleagues (41) investigated the effects of resistance and aerobic training protocols, respectively, on the IGF axis; however in contrast with previous investigations, they provided exploratory analyses into the individual responses of IGFI.

Exercise-induced changes in systemic IGFI from baseline to endpoint (delta percentage values) were linearly correlated ($r = -0.62$, ref. 42; $r = -0.77$, ref. 41) with resting preintervention values.

Table 3. Effects of exercise interventions on IGFBP1, IGFBP2, and IGFBP3

<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>Mean change [Mean (SD)]</th>
<th>$\Delta$ percentage $P$ value</th>
<th>Between groups analysis $P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGFBP1 (ng/mL$^{-1}$)</td>
<td></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)</td>
<td>53.2 (30.4)</td>
<td>NA</td>
<td>5.6 (13.4)</td>
<td>12.0%</td>
<td>NA</td>
</tr>
<tr>
<td>2 Schmitz et al., 2005 (35)*</td>
<td>I: 36.9 (2.9)</td>
<td>34.7 (2.9)</td>
<td>NA</td>
<td>-2.1 (2.3)</td>
<td>-5.8%</td>
<td>NA</td>
</tr>
<tr>
<td>3 Janelins et al., 2011 (32)</td>
<td>I: 72.6 (25.6)</td>
<td>76.4 (42.8)</td>
<td>NA</td>
<td>3.8 (27.3)</td>
<td>5.2%</td>
<td>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%</td>
<td>NA</td>
</tr>
<tr>
<td>IGFBP2 (ng/mL$^{-1}$)</td>
<td></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)</td>
<td>449.6 (29.4)</td>
<td>NA</td>
<td>27.9 (16.8)</td>
<td>6.6%</td>
<td>NA</td>
</tr>
<tr>
<td>IGFBP3 (ng/mL$^{-1}$)</td>
<td></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)</td>
<td>2264.2 (435.4)</td>
<td>NA</td>
<td>103.4 (224.7)</td>
<td>4.8%</td>
<td>NA</td>
</tr>
<tr>
<td>2 Schmitz et al., 2005 (35)*</td>
<td>I: 4339.7 (133.2)</td>
<td>4356.2 (132.7)</td>
<td>NA</td>
<td>-77.1 (315.5)</td>
<td>-3.6</td>
<td>NA</td>
</tr>
<tr>
<td>3 Irwin et al., 2009 (31)*</td>
<td>I: 4150.0 (60.0)</td>
<td>4355.0 (130.0)</td>
<td>NA</td>
<td>165.0 (85.9)</td>
<td>0.4%</td>
<td>NA</td>
</tr>
<tr>
<td>4 Janelins et al., 2011 (32)</td>
<td>I: 39.2 (6.3)</td>
<td>40.1 (7.3)</td>
<td>NA</td>
<td>0.9 (5.1)</td>
<td>2.3%</td>
<td>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>135.3 (83.8)</td>
<td>3.0%</td>
<td>NA</td>
</tr>
<tr>
<td>6 Santa Mina et al., 2013 (34)</td>
<td>I: 1552.7 (514.3)</td>
<td>1770.4 (2579.1)</td>
<td>NA</td>
<td>-131.7 (23.7)</td>
<td>-7.3%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: A, aerobic exercise group; C, control group; I, intervention group; NA, not applicable; R, resistance training group.

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

**Data presented as mean (SE).
IGF1 levels, demonstrating that participants with elevated baseline IGF1 experienced the greatest decrease in response to exercise, whereas those with lower baseline levels of IGF1 experienced increases in response to training. These findings present an intriguing hypothesis for the specific role of exercise in the optimization 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 maximized (43). After this optimization, 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 overabundance, exercise may act to reduce systemic IGF1 levels. This holds particular importance when considering that it is the deregulation and overexpression of IGF1 and IGF2 that is associated with the development and progression of carcinomas. Decreasing IGF concentrations in states of systemic overabundance may effectively reduce IGF1R-mediated signaling that can subsequently improve cancer outcomes through ablation of this mitotic signaling 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 IGF1 and IGFBP3 levels is age. Both IGF1 and IGFBP3 demonstrate a continual increase to a pubertal peak before a gradual decline (47, 48). Accounting for the population age is therefore critical to understanding the normative systemic expression of both IGF1 and IGFBP3 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 to 72 years. Future trials should endeavor to utilize populations of a homogeneous age to reduce variability in the IGF axis related to age, or comparing against age-standardized reference ranges. However, caution should be extended when comparing populations with previously published reference ranges as these are often dependent on the assay method used for analysis, with considerable interassay variation reported (49). In recognition of this interassay variation, an international consensus statement on the standardization of IGF1 quantification was developed, which recommended a common IGF1 standard (02/254) for assay calibration (50). Future trials should ensure that measurements of IGF or any comparisons with reference ranges adhere to these recommendations to ensure accuracy and comparability of results. In the present review, all studies except one (32) used an ELISA method for IGF ligand and binding protein measurement. Reference ranges for measures of IGF1 and IGFBP3 derived from the ELISA method adhering to the consensus statement are currently only available for pediatric populations (51). One set of IGF1 reference ranges published prior to this consensus statement by Andreasen and colleagues (52) utilizing 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 IGF1 levels until more extensive data are published. When considering the IGF1 levels of studies included in this review against this reference range, the decrease in IGF1 reported in the trial by Irwin and colleagues (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 and colleagues (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 and colleagues (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 IGF1 response.

Interpreting changes in IGFBP3 with reference to the baseline values allow for some important observations. Specifically, increases in IGFBP3 tended to be reported in groups with baseline values between 2,000 and 3,000 ng mL$^{-1}$ (29, 33), whereas those that reported decreases had baseline levels of greater than 4,000 ng mL$^{-1}$ (31, 34). The influence of baseline values appears particularly evident in the results reported by Santa Mina and colleagues (34), who demonstrated an IGFBP3 increase in response to resistance training and a decrease in response to aerobic training. Before concluding that differential effects exist between exercise modalities, is should be noted that baseline IGFBP3 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 utilizing the ELISA method, this method of interpretation should only be considered exploratory until further data are available.

IGF1 levels have been positively correlated with measures of body mass index, and although at the population level, this effect was not of sufficient clinical significance to warrant weight-standardized reference ranges (47), at the individual level, this may be important when considering the IGF axis response to exercise. Synthesis of IGF1 occurs in a range of extrahepatic tissues, such as skeletal muscle, bone, cartilage, and adipose tissue (53, 54). Although the main contributor to systemic levels is hepatic production, changes in the volume of tissue producing IGF1 in an autocrine fashion may also translate to systemic alterations. With exercise, systemic IGF1 alterations resulting from autocrine production are primarily concerned with changes in tissues that are also exercise-responsive, such as skeletal myocytes and adipocytes. Increases in skeletal muscle IGF1R density and activation in response to exercise should also be considered as a potential mechanism for reducing systemic levels of IGF1. Skeletal muscle IGF1R density and activation should be interpreted concomitantly with changes of muscle volume, as the surface area of IGF1-permeable myocytes will strongly influence the relationship between exercise and systemic IGF ligand alterations. Although body fat (fat mass or body fat percentage) and muscle volume were reported in 71.4% and 42.9% of studies, respectively, only one study (35) utilized 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 nonlinearity of the IGF axis response to exercise and its relationship to age and body mass may necessitate the inclusion of more individualized 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 IGF1 coefficients of variation in the exercise groups by Fairey and colleagues (29) and Lee and colleagues (33) were 43.2% and 44.5%, respectively. Furthermore, coefficients of variation of the mean changes in systemic IGF1 levels in response to the interventions ranged from 75.9% to 218.4% in the four studies reporting these data (29, 31, 32, 35). Similar variances in the mean changes in IGFBP3 in response to exercise were also reported (42.1%–519.3%; refs. 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 to 3.6 years (31, 33, 35). Average time since treatment was only reported in two studies (29, 35), ranging from 1.1 to 1.2 years. The majority of studies reported information relating to stage of disease (29, 31, 33–35), ranging from 1.1 to 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 stages I to III) as part of the inclusion criteria (29, 31–33). Irwin and colleagues (31) specifically analyzed the effect of breast cancer stage on the IGF axis response. Although 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. Although participants in the included investigations were not currently undergoing surgical, chemotherapeutic, or radiation treatment, current hormone therapy use was prevalent among 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 subanalyses 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 to 17 participants (30, 33), whereas randomized controlled trials ranged from 19 to 85 participants (29, 31, 32, 34, 35). It is strongly recommended that future trials ensure that the sample sizes are sufficient to allow for subanalyses 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 make 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 minimizes 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 subanalyses 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.

**Differential physiologic 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 characterizing the effect of exercise on the IGF axis, it is critical to recognize the noncarcinogenic, 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 physiologic basis by which exercise may influence the systemic IGF axis. Similar to the carcinogenic potential of the IGF axis mediated through IGF1R 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 IGF1 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 IGF1 expression in facilitating anabolic adaptations to exercise. In a liver-specific IGF1–deficient murine model (expressing 70% reductions in systemic IGF1 compared with wild-type models), serological IGF1 deficiency did not impair improvements in muscular performance in response to exercise training (58), whereas intramuscular overexpression of local IGF1 accelerated muscular regeneration after a period of immobilization-induced atrophy in IGF1 normative mice (59). In clinical populations characterized by cachexia and muscular atrophy, local IGF1 has been shown to mediate the anabolic response of skeletal muscle to exercise (60–62). Hambrecht and colleagues (60) demonstrated local muscular IGF1 increased by 81% with no parallel change in systemic IGF1 in response to 6 months of aerobic exercise training [20 minutes/day; 70% maximal oxygen uptake (VO2max)]. Utilizing a progressive resistance training program (3 × 8 repetitions; 80% 1RM; 2 days/week; 24 weeks), Lemmey and colleagues (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 IGF1 and IGFBP3, respectively, whereas no changes in systemic IGF1, IGF2, IGFBP1, or IGFBP3 were observed.

To further explore this relationship, it must be noted that IGF1 is expressed in three specific isoforms: IGFI1Ea, IGFI1Eb, and IGFI1Ec. IGFI1Ea and IGFI1Eb are splice variants typically found in systemic circulation (primarily of hepatic origin), whereas the IGFI1Ec is an autocrine variant exclusively produced locally in myocytes. IGFI1Ec is upregulated in response to mechanical stimuli (e.g., exercise) leading to this isoform being termed mechano-growth factor (MGF; ref. 43). In younger men (29.5 ± 1.5 years), Hameed and colleagues (63) demonstrated acute increases in MGF in response to high-resistance knee extension (10 × 6 repetitions; 80% 1RM) with no changes in IGFI1Ea. Ahtaiinen and colleagues (64) reported acute increases in both MGF and IGFI1Ea in response to heavy-resistance exercise (5 × 10RM leg press and 4 × 10RM squats).

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Conversely, Popov and colleagues (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 IGFI1αa reported in either condition. Although 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 IGF1R has been shown to increase in response to acute resistance exercise (69, 70). Willborn and colleagues (71) demonstrated an identical increase in the expression of muscular IGF1R mRNA in response to both higher intensity (80%–85% 1RM) and lower intensity (60%–65% 1RM) resistance training, peaking 2 hours after exercise and returning to baseline after 6 hours. In the same cohort, Taylor and colleagues (72) demonstrated elevated IGF1R phosphorylation up to 6 hours after exercise in skeletal muscle. It has been reported that during exercise, active skeletal muscle surpasses the liver as the principle producer of systemic IGF1 (autocrine production) and also is the principle extractor of IGF1 from circulation (43, 67). Increases in the expression and activation of the IGF1R may potentiate a transient postexercise period of increased IGF ligand permeability and subsequent cellular signaling. This increase in receptor density and activation suggests a plausible biologic 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 physiologic 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 endeavor to quantify the intramuscular expression of the IGF axis constituents in response to exercise concurrent with systemic changes to determine the exercise-induced response and any differential effects between systems [see the analysis of Lemmey and colleagues (61) for reference].

Conclusions and Summary of Future Directions

This review has several limitations worthy of mention. First, analysis was only completed on published results; relevant unpublished data may have been omitted. Second, this review has focused 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 IGFI 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. Although the pathophysiologic role of the IGF axis in tumor 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 postmalignancy. The majority of studies included in the present review investigated survivorship (postmalignancy) 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 with survivorship populations, there appears to be substantial differences in the IGF axis with current malignancy, with both the systemic and tissue expressions of these factors to be considered. In malignant tissue, the IGF1R is often overexpressed in a number of cancers (74, 75), with the degree of overexpression being correlated with tumor 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). Cancersous tumors are capable of producing IGF ligands in an autocrine or paracrine manner (83); 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 IGFI1R signaling.

Although the development of IGFI1R 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 IGFI1R signaling in selective tissues (54, 86). Alternative strategies include using monoclonal antibodies to reduce the bioavailability of ligands capable of initiating IGFI1R signaling (73). To this end, exercise may be an effective targeted therapy by way of its physiologic potential to reduce systemic IGF ligands capable of IGFI1R activation in conditions of overabundance without adversely affecting the anabolic role of this signaling in skeletal myocytes. In addition, IGFI1R 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 tumor-specific outcomes related to the IGFI1R and its intracellular signaling 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 use a more expansive analysis of the IGF axis to include both its differential roles in systemic and local tissues. In addition, 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 oncolgical treatment.
Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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73. Lodhia KA, Thienchanananda P, Haluska P. Understanding the key to targeting the IGF axis in cancer: a biomarker assessment. Front Oncol 2015;5.


The Influence of Exercise on the Insulin-like Growth Factor Axis in Oncology: Physiological Basis, Current, and Future Perspectives

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