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Review

Cancer Epidemiology, Biomarkers & Prevention

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. 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 physiologic basis and mechanistic underpinnings of the seemingly disparate relationship between exercise and the IGF axis in oncology. Although there is currently insufficient evidence to categorize 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. *Cancer Epidemiol Biomarkers Prev; 25(2); 239–49. ©2015 AACR.*

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 endocrine mechanisms, primarily of hepatic origin but also through paracrine and autocrine mechanisms produced in extrahepatic tissues (11). Transphosphorylation of the IGF1R by the 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 IGF1R 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

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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 in cancerous tissues necessitate 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*, individual*, participant*, patients, 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 ($n = 4250$) and from the literature of an author contained within the reference list of an included article ($n = 1$). A total of seven articles

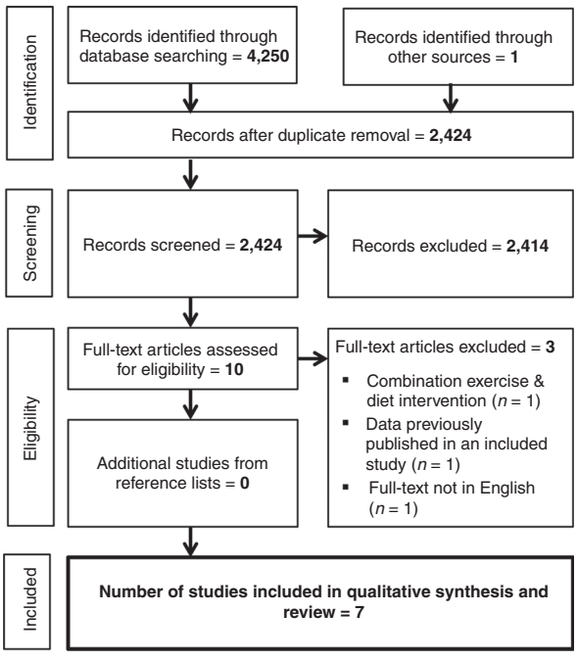

Figure 1.
Consort diagram illustrating the search process.

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 IGF2 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 ($\dot{V}O_2$) 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

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Table 1. Study characteristics

Author, year	Study type	Population [age (years), body mass (kg), BMI (kg.m^{-2}) = mean (SD)]	Exercise prescription			
			Type	Duration (weeks)	Frequency (sessions/week)	Protocol and outcomes (I: intervention; C: control)
1 Fairey et al., 2003 (29)	RCT	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)	A	15	3	I: Cycling at 70–75% $\dot{V}O_2$ peak for 15 minutes; increasing by 5 minutes/3 weeks to a maximum of 35 minutes. Preceded and followed by 5 minutes of cycling at 50% $\dot{V}O_2$ peak; C: No formal intervention; supervised: yes; outcomes: IGF1, IGF2, IGFBP1, IGFBP2, IGFBP3 [ELISA]
2 Schmitz et al., 2005 (35)[a]	RCT	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)	R	26	2	I: 26-week progressive resistance training program; 9 exercises, 3 sets, 8–12 reps completed at 8–10RM (upper body exercises were progressed as able depending on lymphoedema risk and symptoms); C: Delayed treatment; supervised: yes; outcomes: IGF1, IGF2, IGFBP1, IGFBP2, IGFBP3 [ELISA]
3 Irwin et al., 2009 (31)	RCT	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)	A	26	5	I: 15 minutes of moderate intensity aerobic activity (walking) progressing to 30 minutes per session by week 5; C: Usual care; supervised: yes; outcomes: IGF1, IGFBP3 [ELISA]
4 Galvao et al., 2008 (30)	SGI	T: prostate cancer; $n = 10$; age = 70.3 (8.3)	R	20	2	I: Progressive resistance training program; 10 weeks of hydraulic machine–based exercises followed by 10 weeks of isotonic resistance exercises; 10-week blocks distributed as: weeks 1 and 2 = 2 × 12RM, weeks 3 and 4 = 3 × 10RM, weeks 5, 6, and 7 = 3 × 8RM, weeks 8, 9, and 10 = 4 × 6RM; supervised: yes; outcomes: IGF1 [ELISA]
5 Janelsins et al., 2011 (32)	RCT	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)	TC	12	3	I: 60 minutes of Yang-style Tai Chi Chuan (first 15 moves of the long-form Yang-style Tai Chi Chuan). Session included 10-minute warm up, 40 minutes of exercise (Tai Chi), and 10 minutes of breathing, imagery, and meditation; C: Psychosocial therapy; supervised: yes; outcomes: IGF1, IGFBP1, IGFBP3 [IRMA]
6 Lee et al., 2013 (33)	SGI	T: colorectal cancer; $n = 17$ (7 women); age = 55.1 (13.7); body mass = 61.3 (10.6); BMI = 23.1 (3.4)	A and R	12	NR	I: Program to increase weekly physical activity to 18 MET hours/week after 6 weeks and to 27 MET hours/week after 12 weeks; combination of aerobic exercise (walking, cycling) and resistance training; supervised: home-based; outcomes: IGF1, IGFBP1, IGFBP3 [ELISA]
7 Santa Mina et al., 2013 (34)	RCT	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)	A or R	26	5	I (A): 60 minutes of aerobic exercise at 60%–80% HRR; I (R): 60 minutes of progressive resistance training; 10 exercises targeting major muscle groups; 2–3 sets, 8–12 repetitions at 60%–80% 1RM; supervised: home-based; outcomes: IGF1, IGFBP3 [ELISA]

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; $\dot{V}O_2$, volume of oxygen consumed; RM, repetition maximum.
[a]Only RCT component of the study by Schmitz et al. (35) is included in the analysis.

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Table 2. Effects of exercise interventions on IGF1 and IGF2

Author, year	Baseline [1] [Mean (SD)]	1st endpoint [2] [Mean (SD)]	2nd endpoint [3] [Mean (SD)]	Within group analysis			Between groups analysis
				Mean change [Mean (SD)]	Δ percentage	*P* value	*P* value
IGF1 (ng.mL^{-1})							
1 Fairey et al., 2003 (29)	I: 67.4 (29.1)	62.5 (23.9)	NA	−4.9 (10.7)	−7.3%	NA	$P = 0.045$
	C: 70.0 (21.5)	72.6 (24.8)	NA	2.5 (14.8)	3.6%	NA	
2 Schmitz et al., 2005 (35)[a]	I: 172.9 (11.6)	181.2 (11.6)	NA	8.3 (6.3)	4.8%	NA	$P = 0.16$
	C: 194.3 (11.4)	190.3 (11.4)	NA	−4.0 (6.1)	−2.0%	NA	
3 Irwin et al., 2009 (31)[b]	I: 213.3 (12.6)	207.1 (11.2)	NA	−7.4 (6.0)	−2.9%	NA	$P = 0.026$
	C: 232.3 (18.7)	243.7 (18.5)	NA	12.7 (6.4)	4.8%	NA	
4 Galvao et al., 2008 (30)[b]	I: 158.9 (19.4)	161.4 (16.1)	156.3 (14.3)	NA	(1–2) 1.6% (1–3) −1.6% (2–3) −3.2%	$P > 0.05$	NA
5 Janelsins et al., 2011 (32)	I: 156.8 (19.6)	129.5 (43.8)	NA	−27.3 (45.1)	−17.4%	NA	$P > 0.05$
	C: 111.8 (82.6)	95.1 (58.7)	NA	−16.6 (66.5)	−14.9%	NA	
6 Lee et al., 2013 (33)	I: 135.4 (60.2)	159.5 (62.1)	NA	NA	17.8%	$P = 0.007$	NA
7 Santa Mina et al., 2013 (34)	I (A): 159.6 (55.2)	169.7 (67.5)	161.9 (45.9)	NA	(1–2) 6.3% (1–3) 1.4% (2–3) −4.6%	NA	(1–2) $P = 0.129$ (1–3) $P = 0.199$
	I (R): 159.1 (51.2)	138.3 (42.6)	146.4 (49.5)	NA	(1–2) −13.1% (1–3) −8.0% (2–3) 5.9%	(1–2) $P \leq 0.05$	NA
IGF2 (ng.mL^{-1})							
1 Fairey et al., 2003 (29)	I: 824.9 (155.5)	805.0 (139.9)	NA	−19.9 (97.1)	−2.4%	NA	$P = 0.101$
	C: 714.5 (148.9)	735.3 (152.4)	NA	20.9 (80.5)	2.9%	NA	
2 Schmitz et al., 2005 (35)[a]	I: 898.0 (34.9)	871.8 (34.9)	NA	−26.2 (16.7)	−3.0%	NA	$P = 0.02$
	C: 891.3 (34.4)	919.5 (34.4)	NA	28.3 (16.3)	3.2%	NA	

Abbreviations: A, aerobic exercise group; C, control group; I, intervention group; NA, not applicable; R, resistance training group.
[a]Only RCT component of the study by Schmitz et al. (35) is included in the analysis.
[b]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% ($P \leq 0.05$) in prostate cancer patients with no further significant changes after an additional 13 weeks of training. No within-group changes in IGF1 were observed in response to the parallel aerobic training group ($P > 0.05$). A significant increase (17.8%; $P = 0.007$) in IGF1 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 IGF1 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. A second 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 12.1% ($P \leq 0.05$) within-group increase in serum IGFBP3 was observed in response to resistance training and a 23.7% ($P \leq 0.05$) 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

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

Author, year	Baseline [1] [Mean (SD)]	1st endpoint [2] [Mean (SD)]	2nd endpoint [3] [Mean (SD)]	Within group analysis			Between groups analysis
				Mean change [Mean (SD)]	Δ percentage	*P* value	*P* value
IGFBP1 (ng.mL^{-1})							
1 Fairey et al., 2003 (29)	I: 47.5 (32.3)	53.2 (30.4)	NA	5.6 (13.4)	12.0%	NA	$P = 0.774$
	C: 48.2 (29.8)	52.4 (34.2)	NA	4.2 (21.2)	8.7%	NA	
2 Schmitz et al., 2005 (35)[a]	I: 36.9 (2.9)	34.7 (2.9)	NA	−2.1 (2.3)	−5.8%	NA	$P = 0.36$
	C: 36.9 (2.8)	37.8 (2.8)	NA	0.8 (2.3)	2.2%	NA	
3 Janelsins et al., 2011 (32)	I: 72.6 (25.6)	76.4 (42.8)	NA	3.8 (27.3)	5.2%	NA	$P > 0.05$
	C: 92.2 (39.0)	101.3 (50.0)	NA	9.1 (36.4)	9.9%	NA	
4 Lee et al., 2013 (33)	I: 6.2 (5.1)	7.3 (6.3)	NA	NA	17.0%	$P = 0.35$	NA
IGFBP2 (ng.mL^{-1})							
1 Schmitz et al., 2005 (35)[a]	I: 421.7 (29.5)	449.6 (29.4)	NA	27.9 (16.8)	6.6%	NA	$P = 0.30$
	C: 472.9 (29.0)	476.5 (29.1)	NA	3.6 (16.4)	0.8%	NA	
IGFBP3 (ng.mL^{-1})							
1 Fairey et al., 2003 (29)	I: 2160.8 (421.1)	2264.2 (435.4)	NA	103.4 (224.7)	4.8%	NA	$P = 0.021$
	C: 2146.2 (438.2)	2069.1 (478.4)	NA	−77.1 (313.5)	−3.6	NA	
2 Schmitz et al., 2005 (35)[a]	I: 4339.7 (133.2)	4356.2 (132.7)	NA	16.5 (85.9)	0.4%	NA	$P = 0.32$
	C: 4519.7 (130.9)	4655.1 (131.0)	NA	135.3 (83.8)	3.0%	NA	
3 Irwin et al., 2009 (31)[b]	I: 4150.0 (160.0)	3980.0 (160.0)	NA	−190.0 (80.0)	−4.1%	NA	$P = 0.006$
	C: 4480.0 (170.0)	4610.0 (180.0)	NA	150.0 (100.0)	2.9%	NA	
4 Janelsins et al., 2011 (32)	I: 39.2 (6.3)	40.1 (7.3)	NA	0.9 (3.1)	2.3%	NA	$P > 0.05$
	C: 40.8 (13.6)	40.1 (15.1)	NA	−0.7 (3.8)	−1.7%	NA	
5 Lee et al., 2013 (33)	I: 2670.0 (1480.0)	3480.0 (1000.0)	NA	NA	30.3%	$P = 0.013$	NA
6 Santa Mina et al., 2013 (34)	I (A): 5582.7 (1514.3)	4770.4 (2579.1)	4259.8 (1349.2)	NA	(1–2)−14.6% (1–3)−23.7% (2–3)−10.7%	(1–3) $P \leq 0.05$	(1–2) $P = 0.794$ (1–3) $P = 0.043$
	I (R): 4360.5 (1370.9)	4321.3 (1205.5)	4887.9 (1639.7)	NA	(1–2)−0.9% (1–3) 12.1% (2–3) 13.1%	(1–3) $P \leq 0.05$	

Abbreviations: A, aerobic exercise group; C, control group; I, intervention group; NA, not applicable; R, resistance training group.
[a]Only RCT component of the study by Schmitz et al. (35) is included in the analysis.
[b]Data presented as mean (SE).

were remarkably heterogeneous with substantial variation in the magnitude and direction. This heterogeneity of findings extended to changes in IGFBP3 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 IGF1 and IGFBP3. 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 nonlinear and influenced by numerous factors, the complexities of which are discussed below.

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 IGF1 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 (HR_{max}); 5 days/week; 16 weeks] in young women, with no concurrent change in IGF1, IGFBP1, or IGFBP2. In contrast, decreases in systemic IGF1 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 IGF1. Exercise-induced changes in systemic IGF1 from baseline to endpoint (delta percentage values) were linearly correlated ($r = -0.62$, ref. 42; $r = -0.77$, ref. 41) with resting preintervention

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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 with aging (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 Andreassen 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 measures 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.

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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), 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 ($\dot{V}O_2$max)]. 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: IGF1Ea, IGF1Eb, and IGF1Ec. IGF1Ea and IGF1Eb are splice variants typically found in systemic circulation (primarily of hepatic origin), whereas the IGF1Ec is an autocrine variant exclusively produced locally in myocytes. IGF1Ec 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 IGF1Ea. Ahtiainen and colleagues (64) reported acute increases in both MGF and IGF1Ea 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 IGF1Ea 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). Wilborn 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 concurrently 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 IGF1 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). Cancerous tumors 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 IGF1R signaling.

Although the development of IGF1R 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 IGF1R signaling in selective tissues (54, 86). Alternative strategies include using monoclonal antibodies to reduce the bioavailability of ligands capable of initiating IGF1R 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 IGF1R activation in conditions of overabundance without adversely affecting the anabolic role of this signaling in skeletal myocytes. In addition, IGF1R 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 IGF1R 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 oncological treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Wolin KY, Patel AV, Campbell PT, Jacobs EJ, McCullough ML, Colditz GA, et al. Change in physical activity and colon cancer incidence and mortality. Cancer Epidemiol Biomarkers Prev 2010;19:3000–4.
2. Goncalves AK, Dantas Florencio GL, Maisonnette de Atayde Silva MJ, Cobucci RN, Giraldo PC, Cote NM. Effects of physical activity on breast cancer prevention: a systematic review. J Phys Act Health 2014;11:445–54.
3. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. Eur J Cancer 2010;46:2593–604.
4. Liu Y, Hu F, Li D, Wang F, Zhu L, Chen W, et al. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. Eur Urol 2011;60:1029–44.
5. Sax AT, Jenkins DG, Devin JL, Hughes GI, Bolam KA, Skinner TL. The insulin-like growth factor axis: a biological mechanism linking physical activity to colorectal cancer survival. Cancer Epidemiol 2014;38:455–9.
6. Betof AS, Dewhirst MW, Jones LW. Effects and potential mechanisms of exercise training on cancer progression: a translational perspective. Brain Behav Immun 2013;30, Supplement:S75–87.
7. Pollak M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. Nat Rev Cancer 2012;12:159–69.
8. Werner H, Bruchim I. The insulin-like growth factor-I receptor as an oncogene. Arch Physiol Biochem 2009;115:58–71.
9. Buffart LM, Galvao DA, Brug J, Chinapaw MJ, Newton RU. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. Cancer Treat Rev 2014;40:327–40.
10. Annunziata M, Granata R, Ghigo E. The IGF system. Acta Diabetol 2011;48:1–9.
11. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. Nat Rev Cancer 2004;4:505–18.
12. Durai R, Yang W, Gupta S, Seifalian AM, Winslet MC. The role of the insulin-like growth factor system in colorectal cancer: review of current knowledge. Int J Colorectal Dis 2005;20:203–20.
13. Duan C, Ren H, Gao S. Insulin-like growth factors (IGFs), IGF receptors, and IGF-binding proteins: roles in skeletal muscle growth and differentiation. Gen Comp Endocrinol 2010;167:344–51.
14. Haisa M. The type 1 insulin-like growth factor receptor signalling system and targeted tyrosine kinase inhibition in cancer. J Int Med Res 2013;41:253–64.
15. Singh P, Alex JM, Bast F. Insulin receptor (IR) and insulin-like growth factor receptor 1 (IGF-1R) signaling systems: novel treatment strategies for cancer. Med Oncol 2014;31:805.
16. Chi F, Wu R, Zeng YC, Xing R, Liu Y. Circulation insulin-like growth factor peptides and colorectal cancer risk: an updated systematic review and meta-analysis. Mol Biol Rep 2013;40:3583–90.
17. Morris JK, George LM, Wu T, Wald NJ. Insulin-like growth factors and cancer: no role in screening. Evidence from the BUPA study and meta-analysis of prospective epidemiological studies. Br J Cancer 2006;95:112–7.
18. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363:1346–53.
19. Davison Z, de Blacquière GE, Westley BR, May FEB. Insulin-like growth factor-dependent proliferation and survival of triple-negative breast cancer cells: implications for therapy. Neoplasia (New York, NY) 2011;13:504–15.
20. Lahm H, Suardet L, Laurent PL, Fischer JR, Ceyhan A, Givel JC, et al. Growth regulation and co-stimulation of human colorectal cancer cell lines by insulin-like growth factor I, II and transforming growth factor alpha. Br J Cancer 1992;65:341–6.
21. Ngo T, Barnard RJ, Tymchuk C, Cohen P, Aronson W. Effect of diet and exercise on serum insulin, IGF-I, and IGFBP-1 levels and growth of LNCaP cells in vitro (United States). Cancer Causes Control 2002;13:929–35.
22. Barnard RJ, Ngo TH, Leung PS, Aronson WJ, Golding LA. A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. Prostate 2003;56:201–6.
23. Ealey KN, Xuan W, Lu S, Archer MC. Colon carcinogenesis in liver-specific IGF-I-deficient (LID) mice. Int J Cancer 2008;122:472–6.
24. Wu Y, Yakar S, Zhao L, Hennighausen L, LeRoith D. Circulating insulin-like growth factor-I levels regulate colon cancer growth and metastasis. Cancer Res 2002;62:1030–5.
25. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. J Natl Cancer Inst 2002;94:972–80.
26. Firth SM, Baxter RC. Cellular actions of the insulin-like growth factor binding proteins. Endocr Rev 2002;23:824–54.
27. Lof M, Bergstrom K, Weiderpass E. Physical activity and biomarkers in breast cancer survivors: a systematic review. Maturitas 2012;73:134–42.
28. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. J Natl Cancer Inst 2012;104:815–40.
29. Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, Mackey JR. Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and insulin-like growth factor binding proteins in postmenopausal breast cancer survivors: a randomized controlled trial. Cancer Epidemiol Biomarkers Prev 2003;12:721–7.
30. Galvao DA, Nosaka K, Taaffe DR, Peake J, Spry N, Suzuki K, et al. Endocrine and immune responses to resistance training in prostate cancer patients. Prostate Cancer Prostatic Dis 2008;11:160–5.
31. Irwin ML, Varma K, Alvarez-Reeves M, Cadmus L, Wiley A, Chung GG, et al. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale exercise and survivorship study. Cancer Epidemiol Biomarkers Prev 2009;18:306–13.
32. Janelsins MC, Davis PG, Wideman L, Katula JA, Sprod LK, Peppone LJ, et al. Effects of Tai Chi Chuan on insulin and cytokine levels in a randomized controlled pilot study on breast cancer survivors. Clin Breast Cancer 2011;11:161–70.
33. Lee DH, Kim JY, Lee MK, Lee C, Min JH, Jeong DH, et al. Effects of a 12-week home-based exercise program on the level of physical activity, insulin, and cytokines in colorectal cancer survivors: a pilot study. Support Care Cancer 2013;21:2537–45.
34. Santa Mina D, Connor MK, Alibhai SM, Toren P, Guglietti C, Matthew AG, et al. Exercise effects on adipokines and the IGF axis in men with prostate cancer treated with androgen deprivation: a randomized study. Can Urol Assoc J 2013;7:E692–8.
35. Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. Cancer Epidemiol Biomarkers Prev 2005;14:1672–80.
36. Frystyk J. Exercise and the growth hormone-insulin-like growth factor axis. Med Sci Sports Exerc 2010;42:58–66.
37. Gatti R, De Palo EF, Antonelli G, Spinella P. IGF-I/IGFBP system: metabolism outline and physical exercise. J Endocrinol Invest 2012;35:699–707.
38. McTiernan A, Sorensen B, Yasui Y, Tworoger SS, Ulrich CM, Irwin ML, et al. No effect of exercise on insulin-like growth factor 1 and insulin-like growth factor binding protein 3 in postmenopausal women: a 12-month randomized clinical trial. Cancer Epidemiol Biomarkers Prev 2005;14:1020–1.

39. Friedenreich CM, Neilson HK, Woolcott CG, McTiernan A, Wang Q, Ballard-Barbash R, et al. Changes in insulin resistance indicators, IGFs, and adipokines in a year-long trial of aerobic exercise in postmenopausal women. Endocr Relat Cancer 2011;18:357–69.
40. Arikawa AY, Kurzer MS, Thomas W, Schmitz KH. No effect of exercise on insulin-like growth factor-I, insulin, and glucose in young women participating in a 16-week randomized controlled trial. Cancer Epidemiol Biomarkers Prev 2010;19:2987–90.
41. Nishida Y, Matsubara T, Tobina T, Shindo M, Tokuyama K, Tanaka K, et al. Effect of low-intensity aerobic exercise on insulin-like growth factor-I and insulin-like growth factor-binding proteins in healthy men. Int J Endocrinol 2010;2010.
42. Orsatti FL, Nahas EA, Maesta N, Nahas-Neto J, Burini RC. Plasma hormones, muscle mass and strength in resistance-trained postmenopausal women. Maturitas 2008;59:394–404.
43. Schoenfeld BJ. Postexercise hypertrophic adaptations: a reexamination of the hormone hypothesis and its applicability to resistance training program design. J Strength Cond Res 2013;27:1720–30.
44. Borst SE, Vincent KR, Lowenthal DT, Braith RW. Effects of resistance training on insulin-like growth factor and its binding proteins in men and women aged 60 to 85. J Am Geriatr Soc 2002;50:884–8.
45. Nindl BC, Alemany JA, Tuckow AP, Rarick KR, Staab JS, Kraemer WJ, et al. Circulating bioactive and immunoreactive IGF-I remain stable in women, despite physical fitness improvements after 8 weeks of resistance, aerobic, and combined exercise training. J Appl Physiol 2010; 109:112–20.
46. Vitiello MV, Wilkinson CW, Merriam GR, Moe KE, Prinz PN, Ralph DD, et al. Successful 6-month endurance training does not alter insulin-like growth factor-I in healthy older men and women. J Gerontol A Biol Sci Med Sci 1997;52A:M149–54.
47. Bidlingmaier M, Friedrich N, Emeny RT, Spranger J, Wolthers OD, Roswall J, et al. Reference intervals for insulin-like growth factor-1 (igf-i) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. J Clin Endocrinol Metab 2014;99:1712–21.
48. Friedrich N, Wolthers OD, Arafat AM, Emeny RT, Spranger J, Roswall J, et al. Age- and sex-specific reference intervals across life span for insulin-like growth factor binding protein 3 (IGFBP-3) and the IGF-I to IGFBP-3 ratio measured by new automated chemiluminescence assays. J Clin Endocrinol Metab 2014;99:1675–86.
49. Frystyk J, Freda P, Clemmons DR. The current status of IGF-I assays–a 2009 update. Growth Hormone IGF Res 2010;20:8–18.
50. Clemmons DR. Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. Clin Chem 2011;57:555–9.
51. Ertl D-A, Gleiss A, Sagmeister S, Haeusler G. Determining the normal range for IGF-I, IGFBP-3, and ALS: new reference data based on current internal standards. Wien Med Wochenschr 2014;164:343–52.
52. Andreassen M, Nielsen K, Raymond I, Kristensen LØ, Faber J. Characteristics and reference ranges of Insulin-Like Growth Factor-I measured with a commercially available immunoassay in 724 healthy adult Caucasians. Scand J Clin Lab Invest 2009;69:880–5.
53. Klöting N, Koch L, Wunderlich T, Kern M, Ruschke K, Krone W, et al. Autocrine IGF-1 action in adipocytes controls systemic IGF-1 concentrations and growth. Diabetes 2008;57:2074–82.
54. Clemmons DR. Modifying IGF1 activity: an approach to treat endocrine disorders, atherosclerosis and cancer. Nat Rev Drug Discov 2007;6: 821–33.
55. Erselcan T, Candan F, Saruhan S, Ayca T. Comparison of body composition analysis methods in clinical routine. Ann Nutr Metab 2000; 44:243–8.
56. Arcaro A. Targeting the insulin-like growth factor-1 receptor in human cancer. Front Pharmacol 2013;4:30.
57. Philippou A, Halapas A, Maridaki M, Koutsilieris M. Type I insulin-like growth factor receptor signaling in skeletal muscle regeneration and hypertrophy. J Musculoskelet Neuronal Interact 2007;7:208–18.
58. Matheny RW, Merritt E, Zannikos SV, Farrar RP, Adamo ML. Serum IGF-I-deficiency does not prevent compensatory skeletal muscle hypertrophy in resistance exercise. Exp Biol Med (Maywood, NJ) 2009;234: 164–70.
59. Ye F, Mathur S, Liu M, Borst SE, Walter GA, Sweeney HL, et al. Overexpression of insulin-like growth factor-1 attenuates skeletal muscle damage and accelerates muscle regeneration and functional recovery after disuse. Exp Physiol 2013;98:1038–52.
60. Hambrecht R, Schulze PC, Gielen S, Linke A, Möbius-Winkler S, Erbs S, et al. Effects of exercise training on insulin-like growth factor-I expression in the skeletal muscle of non-cachectic patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil 2005;12:401–6.
61. Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum 2009; 61:1726–34.
62. Singh MAF, Ding W, Manfredi TJ, Solares GS, O'Neill EF, Clements KM, et al. Insulin-like growth factor I in skeletal muscle after weight-lifting exercise in frail elders. Am J Physiol Endocrinol Metab 1999;277: E135–43.
63. Hameed M, Orrell RW, Cobbold M, Goldspink G, Harridge SD. Expression of IGF-I splice variants in young and old human skeletal muscle after high resistance exercise. J Physiol 2003;547:247–54.
64. Ahtiainen JP, Lehti M, Hulmi JJ, Kraemer WJ, Alen M, Nyman K, et al. Recovery after heavy resistance exercise and skeletal muscle androgen receptor and insulin-like growth factor-I isoform expression in strength trained men. J Strength Cond Res 2011;25:767–77.
65. Popov DV, Lysenko EA, Bachinin AV, Miller TF, Kurochkina NS, Kravchenko IV, et al. Influence of resistance exercise intensity and metabolic stress on anabolic signaling and expression of myogenic genes in skeletal muscle. Muscle Nerve 2015;51:434–42.
66. Adams GR. Invited Review: autocrine/paracrine IGF-I and skeletal muscle adaptation. J Appl Physiol (Bethesda, Md: 1985) 2002;93:1159–67.
67. Goldspink G. Mechanical signals, IGF-I gene splicing, and muscle adaptation. Physiology 2005;20:232–8.
68. Philippou A, Mardaki M, Halapas A, Koutsilieris M. The role of the insulin-like growth factor 1 (IGF-1) in skeletal muscle physiology. In Vivo 2007;21:45–54.
69. Drummond MJ, Miyazaki M, Dreyer HC, Pennings B, Dhanani S, Volpi E, et al. Expression of growth-related genes in young and older human skeletal muscle following an acute stimulation of protein synthesis. J Appl physiol (Bethesda, Md: 1985) 2009;106:1403–11.
70. Gallagher PM, Touchberry CD, Teson K, McCabe E, Tehel M, Wacker MJ. Effects of an acute bout of resistance exercise on fiber-type specific to GLUT4 and IGF-1R expression. Appl Physiol Nutr Metab 2013; 38:581–6.
71. Wilborn CD, Taylor LW, Greenwood M, Kreider RB, Willoughby DS. Effects of different intensities of resistance exercise on regulators of myogenesis. J Strength Cond Res 2009;23:2179–87.
72. Taylor LW, Wilborn CD, Kreider RB, Willoughby DS. Effects of resistance exercise intensity on extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase activation in men. J Strength Cond Res 2012; 26:599–607.
73. Lodhia KA, Tienchaiananda P, Haluska P. Understanding the key to targeting the IGF axis in cancer: a biomarker assessment. Front Oncol 2015;5.
74. Ouban A, Muraca P, Yeatman T, Coppola D. Expression and distribution of insulin-like growth factor-1 receptor in human carcinomas. Hum Pathol 2003;34:803–8.
75. Ozkan EE. Plasma and tissue insulin-like growth factor-I receptor (IGF-IR) as a prognostic marker for prostate cancer and anti-IGF-IR agents as novel therapeutic strategy for refractory cases: a review. Mol Cell Endocrinol 2011;344:1–24.
76. Hakam A, Yeatman TJ, Lu L, Mora L, Marcet G, Nicosia SV, et al. Expression of insulin-like growth factor-1 receptor in human colorectal cancer. Hum Pathol 1999;30:1128–33.
77. Wu XY, Wu ZF, Cao QH, Chen C, Chen ZW, Xu Z, et al. Insulin-like growth factor receptor-1 overexpression is associated with poor response of rectal cancers to radiotherapy. World J Gastroenterol 2014;20:16268–74.
78. Vadgama JV, Wu Y, Datta G, Khan H, Chillar R. Plasma insulin-like growth factor-I and serum IGF-binding protein 3 can be associated with the progression of breast cancer, and predict the risk of recurrence and the probability of survival in African-American and Hispanic women. Oncology 1999;57:330–40.

79. Khosravi J, Diamandi A, Mistry J, Scorilas A. Insulin-like growth factor I (IGF-I) and IGF-binding protein-3 in benign prostatic hyperplasia and prostate cancer. J Clin Endocrinol Metab 2001;86:694–9.
80. Erarslan E, Coskun Y, Turkay C, Koktener A, Aydogan T. IGF-I levels and visceral fat accumulation in colonic neoplasia. Clin Res Hepatol Gastroenterol 2014;38:99–105.
81. Jiang B, Zhang X, Du LL, Wang Y, Liu DB, Han CZ, et al. Possible roles of insulin, IGF-1 and IGFBPs in initiation and progression of colorectal cancer. World J Gastroenterol 2014;20:1608–13.
82. Renehan AG, Jones J, Potten CS, Shalet SM, O'Dwyer ST. Elevated serum insulin-like growth factor (IGF)-II and IGF binding protein-2 in patients with colorectal cancer. Br J Cancer 2000;83:1344–50.
83. Holdaway IM, Mason BH, Lethaby AE, Singh V, Harvey VJ, Thompson PI, et al. Serum insulin-like growth factor-I and insulin-like growth factor binding protein-3 following chemotherapy for advanced breast cancer. ANZ J Surg 2003;73:905–8.
84. Heidegger I, Massoner P, Sampson N, Klocker H. The insulin-like growth factor (IGF) axis as an anticancer target in prostate cancer. Cancer Lett 2015;367:113–21.
85. Arnaldez FI, Helman LJ. Targeting the insulin growth factor receptor 1. Hematol Oncol Clin North Am 2012;26:527–42, vii–viii.
86. King H, Aleksic T, Haluska P, Macaulay VM. Can we unlock the potential of IGF-1R inhibition in cancer therapy? Cancer Treat Rev 2014; 40:1096–105.

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