

## Review

# The Insulin-like Growth Factor System in Cancer Prevention: Potential of Dietary Intervention Strategies

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## Abstract

The insulin-like growth factor (IGF) system is related to proliferation and tumor growth, and high levels of circulating IGF-I are thought to be a risk factor for several types of cancer. This review summarizes the epidemiologic evidence for an association between circulating IGF-I and cancer risk as well as the experimental evidence for a causal relation between the endocrine IGF system and tumor growth. The potential for dietary intervention to alter the IGF system and thereby cancer risk is supported by several lines of evidence. Postulated mechanisms of action are as follows: (a) reduction of levels of circulating IGF-I, which will decrease activation of the IGF-I receptor and subsequent signaling pathways; (b) increasing local IGF binding proteins, which may have IGF-dependent effects through obstruction of IGF interaction with local IGF-I receptor as

well as IGF-independent effects; and (c) interference with estrogens and estrogen receptor action, which may have direct (and possibly synergistic) effects on IGF signaling. An overview is given of the epidemiologic studies on dietary determinants of circulating IGF-I. Examples of dietary factors, such as dairy protein, lycopene, and phytoestrogens, are used to illustrate the potential mode of action of dietary interventions that may act on the IGF system. In conclusion, the IGF system has every potential to serve as an intermediate for cancer (chemo)prevention studies. On the short term, more research initiatives aimed at the effects of specific food components or dietary strategies on the IGF system both in animal models and in humans are warranted. (Cancer Epidemiol Biomarkers Prev 2005;14(1):195–203)

## Introduction

The primary role of the human growth hormone-insulin-like growth factor (IGF) axis is the regulation of both prenatal and postnatal growth (1, 2). Recent studies point out that the insulin-IGF signaling pathway, which has been conserved in yeast, worms, fruit fly, mice, and humans, may be causally linked to aging and longevity (3). Besides regulation of normal growth and aging, the IGF system is also involved in carcinogenesis (Fig. 1; ref. 4). Observational epidemiologic studies suggest that circulating levels of IGF-I and its main binding protein [IGF binding protein-3 (IGFBP-3)] are related to the risk of several epithelial cancers (for a systematic review and meta-regression analysis of the published literature until 2002, see ref. 5). In particular, the results of large prospective studies consistently show higher risk of breast and prostate cancer, and possibly colon and lung cancer, in individuals with relatively high levels of IGF-I. Variation in circulating IGF-I levels is thought to be due to both genetic effects and environmental or lifestyle factors. Furthermore, the IGF system is known to interact with insulin (as reviewed in ref. 6) and estrogens at various levels. Animal model systems as well as analyses of human tissue show that the expression of several components of the IGF system may be deregulated in specific tissues and that normal IGF signaling is disrupted during one or more stages of the carcinogenic process.

In light of recent findings on the association between endocrine and paracrine/autocrine IGF systems and carcinogenesis and on the association between lifestyle factors and circulating IGF system components, we will provide the rationale for a role of circulating IGF system components in cancer prevention. Several potentially cancer-preventive dietary strategies will be highlighted, including the mechanisms by which they may influence the IGF system and thereby cancer risk.

## Overview of the Epidemiology

In recent years, many reports have been published on the association between circulating levels of IGF-I and the risk of several types of cancer. In Fig. 2, we summarize the prospective cohort studies as well as those case-control studies that included at least 100 cancer cases. Most valuable are prospective cohort studies especially if blood samples are drawn well before cancer diagnosis. A positive association in such a prospective study would be indicative of circulating IGF-I as a risk factor for cancer. It should be noted that due to the retrospective design of case-control studies, any association found in these studies could be caused by the presence of the tumor.

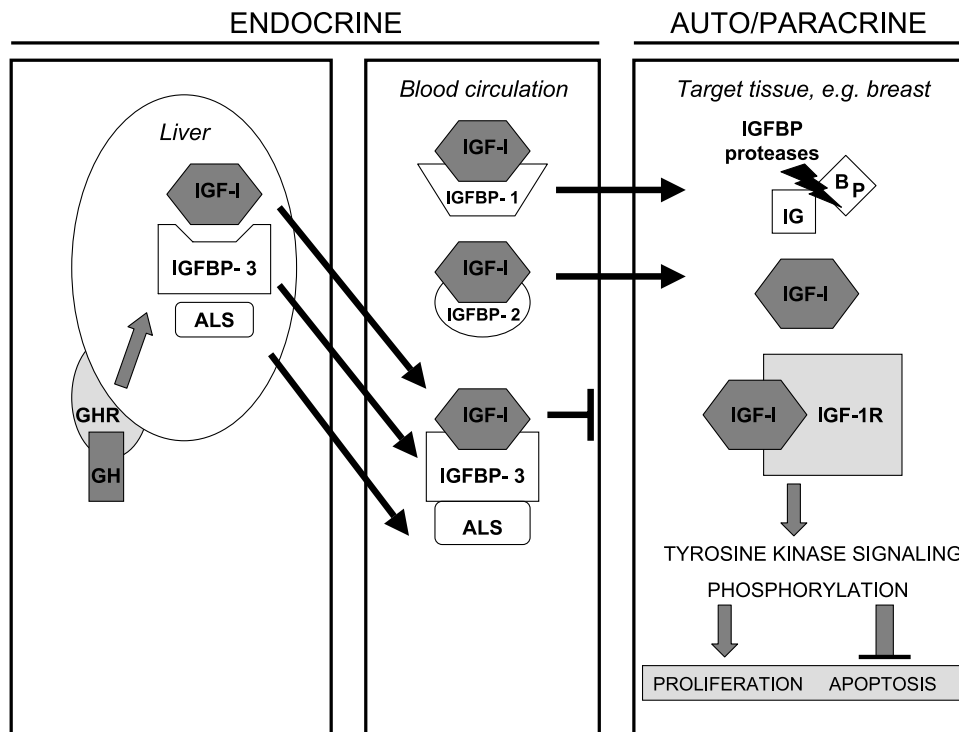
In women, the most consistent positive association with IGF-I has been observed for breast cancer in (young) premenopausal women (i.e., relatively high IGF-I associated with increased cancer risk; refs. 7–13). None of the studies on postmenopausal breast cancer observed a positive association (7–15). The fact that the association is absent in postmenopausal women who have very low estrogen levels suggests that the cancer-promoting effect of IGF-I is enhanced by estrogens. A synergistic effect of IGF-I and sex steroids on breast cancer risk was confirmed in a population-based case-control study by Yu

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**Figure 1.** The circulating and tissue IGF system components. Growth hormone stimulates the liver to synthesize IGF-I, IGFBP-3 (its main binding protein in circulation), and acid-labile subunit (ALS). About 90% of IGF-I in the circulation is bound to IGFBP-3 and acid-labile subunit in a complex too large to pass the capillary endothelium. Free IGF-I (<1%) and IGF-I bound to IGFBP-1 or IGFBP-2 can be transported out of the bloodstream to specific target tissues. IGFBPs, both in the circulation and in tissues, are degradable by proteases, rendering IGF-I free to interact with IGF-IR. Binding to IGF-IR results in receptor phosphorylation, activation of downstream targets, and stimulation of proliferation and inhibition of apoptosis.

et al. (16). The results on the association with IGFBP-3, the main IGFBP in the circulation, are somewhat inconsistent with four of six studies suggesting a similar positive association with premenopausal breast cancer risk (8-13). Prostate cancer, the most frequently occurring hormone-related cancer in men, is also found to be associated with higher circulating levels of IGF-I in the majority of studies (17-24), especially in relatively young men (18, 21). A recent update of the prospective cohort study by Chan et al. (25) suggests that the positive association between IGF-I and prostate cancer risk is limited to advanced-stage prostate cancer. Shi et al. (26) have published a meta-analysis of 14 epidemiologic studies on prostate cancer risk, including 7 case-control studies with <100 cases, and reported an increased risk of prostate cancer associated with high concentrations of serum IGF-I [odds ratio (OR), 1.5; 95% confidence interval, 1.3-1.7] as well as IGFBP-3 (OR, 1.2; 95% confidence interval, 1.0-1.5). All six cohort studies (27-32) on the association between colorectal cancer risk and the circulating IGF system found a positive association (i.e., OR, 1.5), although only two were statistically significant and only after adjustment for IGFBP-3 (27) or when analyses were limited to colon cancer (31). Interestingly, two studies reported on the association with IGF-II and both found a positive association, one of which was statistically significant (28, 33). The results with respect to IGFBP-3 are inconsistent: two studies report a significant inverse association (i.e., protective effect; refs. 27, 29) and two studies report a significant positive association (28, 30). Lung cancer risk has also been studied in relation to serum IGF-I concentrations, but again results are inconsistent, especially those from the prospective cohort studies (34-39). Bladder cancer risk has also been significantly associated with high IGF-I levels (40). Two studies have investigated the association

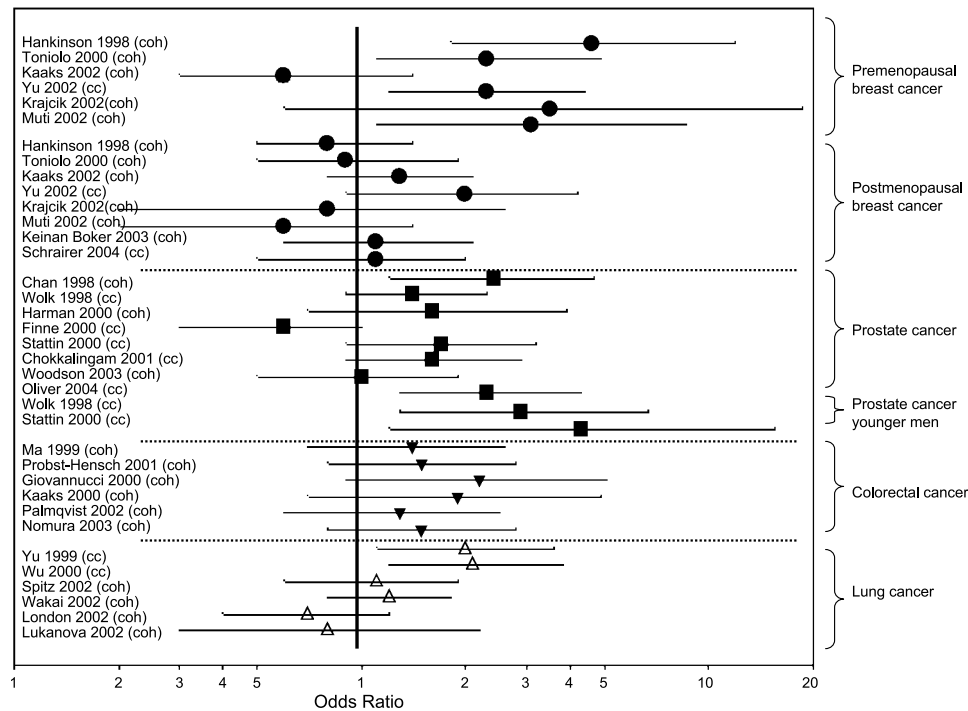
between endometrial cancer and circulating IGF-I levels and found no significant association (41, 42). Overall, a 2-fold increased risk of prostate cancer, premenopausal breast cancer, and possibly colon cancer can be expected in individuals with serum IGF-I levels above the 75th percentile.

Besides the evidence for an association with cancer risk, several studies have been published that show a similar association of serum IGF-I levels with mammographic breast density (43) and precursor lesions, such as ductal carcinoma *in situ* (44), proliferation of colorectal mucosa (45), colorectal adenomas (29, 46, 47), and benign prostatic hyperplasia (48, 49). Obviously, these studies support the evidence for a causal role of increased serum concentrations of IGF-I in one or more stages of the development of several malignancies.

In this respect, it should be noted that relatively high IGF-I levels have also been associated with several possible health benefits, such as decreased risk of cardiovascular disease (50), osteoporosis (51), and less cognitive decline with age (52). Therefore, intervention aimed at reducing IGF-I levels will be especially applicable to individuals at high risk of developing cancer.

### Rationale for Cancer Prevention Strategies Aimed at the IGF System

The strongest evidence for a causal association between circulating IGF-I concentrations and cancer risk comes from animal models. In LID mice, the *igf1* gene is deleted exclusively in the liver, leading to dramatically reduced serum levels of IGF-I (75% decrease) but normal growth and development (53). These mice have delayed onset of chemically



**Figure 2.** ORs (markers) and 95% confidence intervals (horizontal lines) for cancer risk (cancer death in *Wakai 2002*) in individuals with IGF-I concentration in highest quantile versus lowest quantile. Only prospective cohort (nested case-control) studies (coh) are included as well as those case-control studies (cc) that included at least 100 cancer cases. Depicted are the ORs that were adjusted for covariates but not for IGFBP-3 (*Giovannucci 2000*, *Nomura 2003*, and *Wu 2000* were adjusted for IGFBP-3; unadjusted ORs were not reported). Premenopausal breast cancer risk is reported for premenopausal women aged <50 years by *Hankinson 1998* and *Toniolo 2000* and for all women aged <50 years by *Kaaks 2002*.

and genetically induced mammary tumors (54). When receiving colon tumor transplants, LID mice develop less colon tumors and liver metastases than wild-type mice (55). A less dramatic reduction in serum IGF-I (25% decrease) due to energy restriction also decreased malignant transformation in a mouse model, whereas restoration of IGF-I concentrations by recombinant IGF-I stimulated cell proliferation (56). Besides energy restriction, several other dietary or pharmaceutical interventions in animal models have been shown to result in changes in serum levels of IGF system components, thereby altering tumor growth, apoptosis, and other processes related to cancer risk. Several examples of such studies will be described in the next paragraph.

Clearly, the number of experimental animal studies on the IGF system in cancer prevention is increasing. Although the results of these studies cannot be easily generalized to humans, it will help elucidate the underlying mechanisms. Overall, the current evidence from studies in model systems points to the IGF system as a feasible cancer prevention target. If variation in circulating levels of (free) IGF-I is also causally associated with cancer risk in humans, even marginal alterations in the serum concentration of IGF system components may provide an interesting contribution to cancer prevention. To further investigate the potential of diet and the IGF system in cancer prevention, two questions need to be addressed. First, intervention studies are needed to investigate whether the concentration of (free) circulating IGF-I in humans is modifiable by exogenous factors, such as lifestyle changes or pharmaceutical/dietary intervention. Second, the effect of marginal changes in serum IGF-I concentrations in humans needs to be studied in relation to the risk of several types of cancer as well as their precursor lesions.

With respect to the first question, it is not yet clear which factors determine the circulating levels of IGF system components in humans. Genetic variation is estimated to account for

40% to 60% of the total variation in circulating levels of IGF-I and IGFBPs (57, 58). Therefore, ~50% of the variation should, in principle, be modifiable by exogenous factors (e.g., dietary habits or other lifestyle factors). Manipulation of the insulin pathway may well have beneficial effects on the IGF system (6). Many studies have investigated the association between physical activity and the IGF system, although the results remain inconsistent (59). It is a well-known phenomenon that, in cases of chronic or acute energy restriction, serum levels of IGF-I are strongly reduced (60, 61). However, the evidence with regard to most dietary factors in humans is limited to observational epidemiologic studies (62-74). In Table 1, we summarize the evidence from studies on animal models and from cross-sectional and experimental studies in humans. The evidence is inconclusive on all dietary factors, although it suggests that energy and alcohol intake within the normal range are not associated with IGF-I. This summary table suggests the following: (a) intake of animal protein and dairy products may possibly be positively associated, and intake of some minerals is probably positively associated, with IGF-I; (b) consumption of tomato products and/or intake of lycopene may be inversely associated with IGF-I (or the ratio of IGF-I/IGFBP-3) and positively associated with IGFBP-3; however, the evidence is insufficient; and (c) with respect to consumption of soy and/or intake of isoflavones, the evidence remains insufficient (i.e., they may have opposing effects that could not be disentangled in studies conducted thus far).

Besides these studies of lifestyle factors, some promising pharmaceutical interventions, such as selective estrogen receptor (ER) modulators (e.g., tamoxifen), synthetic retinoic acids (e.g., fenretinide), and cyclo-oxygenase 2 inhibitors (e.g., celecoxib), have also been associated with the IGF system in model systems and are currently being evaluated in clinical trials. Although the IGF system is not the main end point in these trials, they can provide additional insight

into the mechanisms involved in humans. Obviously, such pharmaceutical interventions may prove to be only suitable and acceptable for individuals at very high risk, or those already diagnosed with cancer, and may not be desirable for primary prevention in healthy individuals.

## Understanding Dietary Mechanisms

The relationship between concentrations of IGF-I and its binding proteins in the circulation and tissue expression/content of IGF system components, as well as the mechanisms

**Table 1. Summary of the evidence for associations between dietary factors and serum IGF-I**

Nutrient/food group	Studies using animal models*	Cross-sectional studies in humans†	Experimental studies in humans*	Conclusion
Energy	Severe energy restriction results in 25% decreased serum IGF-I (review; ref. 75)	No association (8×; refs. 68, 63, 69, 71, 66, 72, 73, 74)  Positive association (2×; refs. 67, 70)	Serum IGF-I is markedly lowered by energy deprivation (review; ref. 60)	Probable; positive association with extremes of energy intake  No association within normal range of energy intake
Protein (total or animal)	Severe protein restriction results in 50% decreased serum IGF-I (review; ref. 61)	No association with total and/or animal protein (6×; refs. 64, 66, 71, 73, 74)  Positive association with total or animal protein (5×; refs. 63, 67, 68, 69, 70)	Serum IGF-I is markedly lowered by protein deprivation (review; ref. 60)	Possible; positive association with intake of animal protein
Alcohol	Chronic alcohol feeding may increase or decrease serum IGF-I	No association with IGF-I (5×; refs. 64, 67, 68, 72, 74)  Minor inverse association (66)  Positive association (in men only; ref. 62)	Decline in serum IGF-I after drinking alcohol (1 d only)	No association within normal range of alcohol consumption
Minerals (total or zinc)	Mineral (e.g., zinc, copper, and magnesium) deficiency is associated with low serum IGF-I levels	No association with zinc (68)  Positive association with zinc (63, 67)  Positive association with combined intake of five minerals (including zinc; ref. 69)	Zinc supplementation: increased serum IGF-I levels in specific populations (anemic, non-insulin-dependent diabetes mellitus)	Probable; positive association with zinc or a combination of minerals (including supplements)
Dairy products	Only studies relating to IGF-I content in milk (review; ref. 79)	No association with total dairy (64, 66, 68, 71; one positive association with milk only; ref. 71)  Positive association with total dairy (67)  Positive association with milk (65, 69)	Serum IGF-I increased 10% with three servings of dairy daily (77)	Possible; positive association with consumption of dairy/milk
Soy or isoflavones	Decrease in serum IGF-I in animals on soy protein/phytoestrogen diet (93, 94)	Asian populations: no association with soy or isoflavones (72); positive association (in men only; ref. 73)  European population (including vegans/vegetarians): no association with soy protein (borderline positive with soy milk; ref. 68)  European population (low intake): no association with soy or isoflavones (74)	Soy protein vs. milk protein: stronger increase in IGF-I in soy protein group (99, 100)  Soy protein with vs. without isoflavones: trend towards lower IGF-I with isoflavones (postmenopausal women only; ref. 98) or no difference between groups (101)	Insufficient; association could be positive or inverse, depending on dose and population  Effects of soy protein and isoflavones/phytoestrogens need to be disentangled (possibly opposite effects)

(Continued on the following page)

**Table 1. Summary of the evidence for associations between dietary factors and serum IGF-I (Cont'd)**

Nutrient/food group	Studies using animal models*	Cross-sectional studies in humans†	Experimental studies in humans*	Conclusion
Tomatoes or lycopene	Increased plasma IGFBP-3 concentration in ferrets receiving lycopene (8)	Tomato products: no association (64, 71, 74; 1× inverse with IGF-I/IGFBP-3 ratio; ref. 71); inverse association (66) Lycopene intake: no association (positive with IGFBP-3; ref. 67)	Lycopene intervention: IGF-I decreased in both intervention and control groups (85)	Insufficient; inverse association with IGF (or IGF/IGFBP-3 ratio); positive association with IGFBP-3

NOTE: "Probable": The association (or lack of) is consistently shown in cross-sectional studies and confirmed by experimental studies in animals and in humans. "Possible": Association in some but not all cross-sectional studies; experimental studies in animals consistently show the association; however, no or only one experimental study in humans is available. "Insufficient": Only very few studies have been conducted and these are not entirely consistent.

\*References are only included if a review article is available or if literature is limited to one or two studies.

†All published cross-sectional studies ( $n = 13$ ) are included; references of studies including >500 individuals are printed in bold.

through which both may be related to cancer risk in humans, have not been clarified. Certainly, circulating levels of IGF-I and its binding proteins have endocrine effects on specific target tissues. Additionally, they may be markers of overall tissue expression of these IGF system components, thus reflecting paracrine/autocrine IGF effects. Alternatively, regulation of the circulating and tissue IGF systems may be (partly) independent.

How might dietary factors be able to influence circulating IGF system components and/or tissue IGF systems in humans? Many hypothetical mechanisms can be proposed (Fig. 3). First, as 80% of circulating IGF-I are synthesized in the liver, the most obvious hypothesis would be that exogenous factors directly influence hepatic (or overall tissue) IGF-I expression, synthesis, and secretion, resulting in altered serum levels. Second, the diet may interfere through alteration of IGFBP levels, thereby influencing the ability of IGFs to bind to the IGF-I receptor (IGF-IR) and its resulting signaling cascade. Third, dietary factors may indirectly affect the IGF system through its interaction with estrogen action and/or ER signaling. Each of the above-postulated mechanisms are described in the sections below, including examples of potential dietary determinants and the available evidence from *in vitro* studies, animal models, and studies in humans.

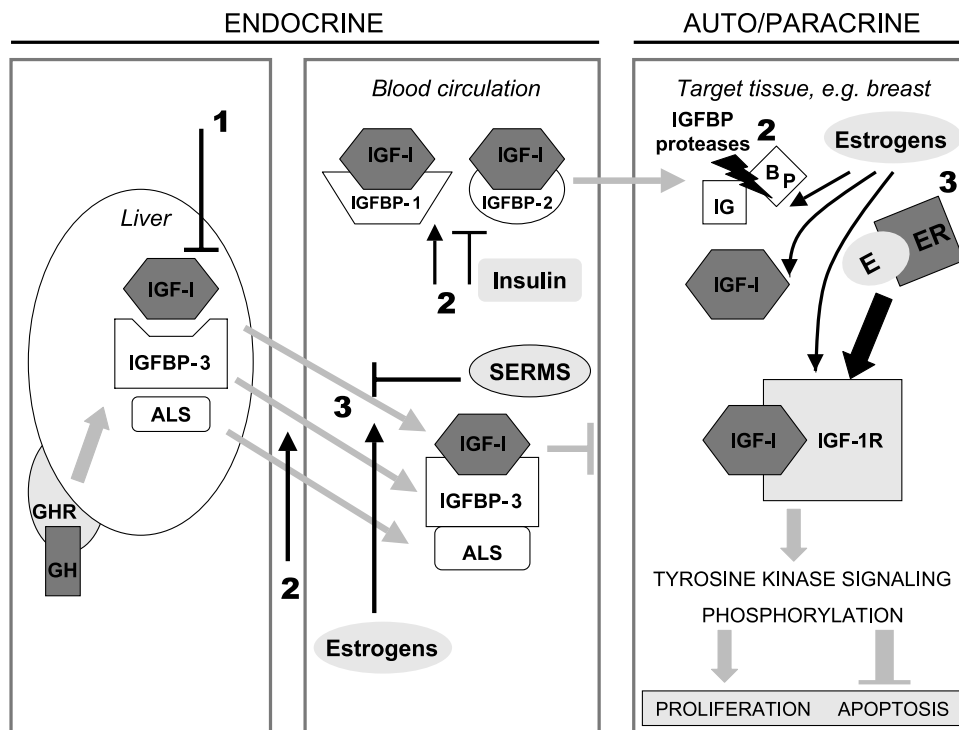
**Effects on Circulating IGF-I.** Hepatic IGF-I expression and thus circulating IGF-I levels may be influenced by exogenous factors either directly or indirectly. Because growth hormone stimulates the liver to produce a large proportion of circulating IGF-I, indirect inhibition of hepatic IGF-I expression/synthesis may occur through decreased growth hormone receptor binding or post-receptor resistance to growth hormone. Reduced steady-state levels of hepatic mRNA for IGF-I (due to reduced mRNA synthesis or enhanced degradation) or reduced translation of IGF-I mRNA to protein will reduce serum IGF-I and may result in altered IGF-signaling in specific tissues through changes in the amount of IGF-I available for receptor binding.

The decreased serum IGF-I levels observed after chronic or acute energy restriction (60, 61, 75) are found to be mainly due to effects on liver IGF-I mRNA levels, although reductions have also been observed in most other tissues studied (60). Dietary administration of corticosterone, which is usually increased during energy restriction, not only resulted in decreased plasma IGF-I concentrations in a rat mammary carcinogenesis model but also in reduced IGF-1R levels in mammary carcinomas, inhibition of several downstream signaling pathways, and reduced incidence of carcinomas (76).

Dairy protein is another example of a dietary factor that is thought to affect serum IGF-I levels in humans possibly through hepatic stimuli. Several cross-sectional studies have found that serum IGF-I concentrations are positively associated with protein intake (63, 69, 70), specifically animal and soy protein (67, 68). In four such studies, consumption of dairy products, a source of animal protein, was positively associated with serum levels of IGF-I (65, 67, 69, 71). In a human intervention study with three servings of dairy products daily, a 10% increase in serum IGF-I was observed (77). From these epidemiologic studies, it cannot be concluded which component in dairy foods might be responsible for this effect and through which mechanism. It may be due to the relatively high level of essential amino acids in dairy protein, resulting in increased hepatic IGF-I synthesis. Studies that tried to disentangle the effects of calcium and dairy protein have been inconsistent (65, 67, 71). Some investigators suggest that the effects of dairy could be due to bovine IGF-I, which is identical to human IGF-I (78) and may be absorbed in humans resulting in a direct increase in serum IGF-I (79).

**IGFBPs and IGF Signaling.** In the circulation, 80% to 90% of IGF-I are bound to IGFBP-3 and acid-labile subunit in a complex too large to exit the bloodstream, whereas only <5% of IGF-I are bound to IGFBP-1 or IGFBP-2 in smaller complexes that facilitate transport to other tissues (Fig. 1). At the cellular level, formation of complexes between IGF-I and any of its binding proteins prevents IGF-I from binding to IGF-1R, thus inhibiting IGF signaling. Dietary factors may influence the IGF system by affecting transcription or degradation of IGFBPs (Fig. 3). For example, dietary energy restriction not only decreases serum IGF-I concentrations but also decreases serum IGFBP-3 concentrations and increases serum IGFBP-1 and IGFBP-2, potentially resulting in accelerated clearance of IGF-I (i.e., more rapid distribution of IGF-I into tissues; ref. 61). The exact role of the main IGFBPs in serum (IGFBP-3, IGFBP-2, and IGFBP-1, respectively) in the regulation of both endocrine and paracrine/autocrine IGF-I action is largely unknown, making it difficult to interpret the effects of dietary factors on IGFBPs.

One example of a dietary factor that may exert its cancer-preventive actions by influencing IGFBPs is lycopene, a tomato-derived substance. Many experimental studies have shown that lycopene can induce cell cycle arrest (80). Several studies show that this effect may (in part) reflect an effect on the IGF system. In 1995, Levy et al. (81) showed that lycopene inhibits basal cell proliferation (measured by thymidine incorporation) in endometrial, lung, and mammary cancer cell lines. More specifically, IGF-I-stimulated growth in endometrial cancer cell lines was repressed by lycopene. Karas et al. (82) showed that growth stimulation of MCF7 mammary cancer cells by IGF-I was also reduced by lycopene. Moreover, in this system, lycopene was shown to



**Figure 3.** Potential mechanisms of direct or indirect effects of exogenous factors on the IGF system. The first potential mechanism represents effects on the levels of circulating IGF-I. The most obvious pathway through which this may occur is through inhibition of hepatic IGF-I synthesis (1). A second mechanism through which IGF signaling might be altered is indirectly through effects on IGFBPs. For instance, synthesis of (hepatic) IGFBP-3 may be stimulated, levels of insulin and other hormones may affect IGFBP-1 and IGFBP-2 levels, and IGFBP degradation may be influenced through effects on proteases (2). The third possible mechanism involves estrogens and the ER: they can affect almost every possible component as well as the interaction between components in the IGF system (3).

inhibit activation of the IGF-1R (i.e., reduced tyrosine phosphorylation of the activator protein 1 transcription complex). This was not due to alterations in the number or affinity of IGF receptors but to increased amounts of membrane-associated IGFBPs. A recent study of lycopene in an experimental animal model (ferrets) reported effects on the endocrine IGF system (i.e., increased serum IGFBP-3 and decreased serum IGF-I/IGFBP-3 ratio) as well as on cancer development (i.e., induction of apoptosis and fewer smoke-induced squamous metaplasia in the lungs; ref. 83).

In 1999, Giovannucci (84) reviewed the epidemiologic studies on intake of lycopene (or tomato products as its major source) and cancer risk. A total of 72 studies were identified, the majority of which reported inverse associations between tomato intake or blood lycopene level and the risk of cancer at a defined anatomic site, most consistently for prostate, lung, and stomach cancer.

Lycopene is a known quencher (the most efficient of all carotenoids) of singlet oxygen and free radicals. Therefore, lycopene is often thought to decrease cancer risk through a reduction in oxidative damage. However, the experimental evidence described in the previous paragraph suggests that alternative pathways, such as the IGF system, may be possible. The number and quality of human studies on the effects of lycopene on the IGF system are insufficient. In one small clinical trial of lycopene supplementation, a reduction in plasma IGF-I and IGFBP-3 levels was observed (85). However, as the serum lycopene concentrations did not significantly increase, the changes to the IGF system may well be due to chance. In cross-sectional epidemiologic studies, high consumption of cooked tomatoes was associated with low serum

IGF-I levels (66) and high lycopene intake was associated with high IGFBP-3 levels (67).

Altogether, the available evidence thus far suggests that lycopene may alter serum/tissue levels of IGFBPs, thereby indirectly influencing bioactive IGF-I levels and IGF signaling. Future experimental studies both in animal models and in humans should incorporate assessment of IGFBP levels as well as the concentration of free IGF-I in the circulation.

**Interaction with Estrogen and ER Activity.** Besides direct dietary effects on components of the IGF system, there may be indirect influences through estrogen and ER signaling (Fig. 3). Estrogen action is strongly related to the IGF system with evidence for cross-talk between the two systems at several levels: Expression of most IGF system components is altered by estradiol (E<sub>2</sub>), the IGF-1R is directly activated by liganded ER, IGF signaling transcriptionally activates the ER, and IGF-I and estrogen have synergistic effects on cell cycle signaling cascades and proliferation (86).

Studies on the serum IGF-I-reducing effects of tamoxifen provide proof of principle for the action of selective ER modulators on the IGF system (87-90). Phytoestrogens (e.g., isoflavones from soy) are also thought to act like selective ER modulators. Moreover, some epidemiologic observational studies have also shown that the risk of several types of cancer is decreased in populations with high intake of soy products (91, 92). The proposition that phytoestrogens may also interfere with the IGF system is mainly derived from these known effects of estrogen and selective ER modulators. Thus far, there is limited direct evidence for an inhibiting effect of phytoestrogens on

IGF-I concentrations or IGF system signaling (93). Zhou et al. (94) found a decrease in serum IGF-I and inhibition of growth of transplantable human prostate carcinoma in mice on a soy protein/phytoestrogen diet. Mentor-Marcel et al. (95) found reduced tumor formation in a rat prostate cancer model on an isoflavone-enriched diet, and Lamartiniere et al. (96) described the down-regulation of expression of androgen receptor, ER, progesterone receptor, and IGF-I mRNA in these rats. Flaxseed, another source of phytoestrogens (i.e., lignans), was also observed to down-regulate IGF-I expression in a nude mice model (97).

Four intervention studies in humans have thus far investigated the IGF effects of soy protein with isoflavones in comparison with either milk protein or soy protein without isoflavones (98-101). The two small parallel studies of soy protein versus milk protein in men and postmenopausal women ( $n < 50$ ) observed increased levels of serum IGF-I in both intervention groups but a significantly stronger increase in the soy protein group (99, 100). A small crossover study included both premenopausal and postmenopausal women; in the premenopausal women, a marginal increase in IGF-I in the low isoflavones but not in the high isoflavones period was observed (98). In contrast, in post-menopausal women, a trend toward decreased IGF-I levels with increasing isoflavone consumption was observed. In a mixed population ( $n = 150$ ), during a 1-year intervention, no change in IGF-I levels was observed in the high isoflavones group nor in the control group that received soy protein without isoflavones (101). Part of the inconsistency between these studies may be due to chance (i.e., small sample size) or to differences in effect between men and women, and between premenopausal and postmenopausal women, possibly due to interactions with endogenous estrogens. Additionally, opposing effects have been suggested for soy protein (IGF-I increasing) and isoflavones (IGF-I decreasing), which would be difficult to disentangle in studies using soy protein products as a source of isoflavones. Further insight may be provided by studies that do not use soy protein but use isoflavone extracts (e.g., from soy or red clover).

## Conclusions

Prospective epidemiologic studies have shown that individuals with relatively high serum concentrations of IGF-I are at increased risk of prostate, colon, and premenopausal breast cancer. Abundant experimental evidence is available for an important role of the IGF system in promoting cancer growth. Evidence for a causal association between the circulating IGF system and cancer in humans is still missing, but such evidence from animal models is accumulating rapidly. Additionally, the number of studies that suggest that the circulating IGF system can be altered by dietary interventions, in a direction that may help prevent cancer, is increasing. This includes observational studies in humans that show that certain specific dietary factors may be associated with the concentration of IGF system components in serum, although the results of these studies are not entirely consistent. Experimental studies in animal models show that dietary intervention affects serum IGF system components as well as the occurrence of cancer in these animals.

IGF-related mechanisms by which dietary interventions, such as energy restriction, lycopene supplementation, and phytoestrogen supplementation, may reduce cancer risk are inhibition of circulating IGF-I-induced proliferation and tumor growth, obstruction of IGF signaling in target tissues by increasing local IGF-BPs and thus decreasing IGF-1R activity, and interference with estrogen and ER action that affects IGF signaling.

In conclusion, the IGF system has high potential to serve as an intermediate system that can be altered to decrease cancer risk by means of possibly more than one dietary intervention strategy. Additional research is needed. First, dietary intervention studies of relatively short duration should be conducted in relevant human populations to investigate, in a highly controlled manner, the effect of such interventions on serum concentrations of total and free IGF-I and of IGFBP-1, IGFBP-2, and IGFBP-3. Where possible, tissue-specific effects on IGF system components and signaling should also be studied in humans. Experimental studies in model systems can help decide which dietary strategies are most effective. In a later stage, this may accumulate to enough evidence to conduct large, long-term human intervention studies with precursor lesions and eventually cancer as the end points.

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