REVIEW

Role of the Insulin-Like Growth Factor Family in Cancer Development and Progression

Herbert Yu, Thomas Rohan

The insulin-like growth factors (IGFs) are mitogens that play a pivotal role in regulating cell proliferation, differentiation, and apoptosis. The effects of IGFs are mediated through the IGF-I receptor, which is also involved in cell transformation induced by tumor virus proteins and oncogene products. Six IGF-binding proteins (IGFBPs) can inhibit or enhance the actions of IGFs. These opposing effects are determined by the structures of the binding proteins. The effects of IGFBPs on IGFs are regulated in part by IGFBP proteases. Laboratory studies have shown that IGFs exert strong mitogenic and antiapoptotic actions on various cancer cells. IGFs also act synergistically with other mitogenic growth factors and steroids and antagonize the effect of antiproliferative molecules on cancer growth. The role of IGFs in cancer is supported by epidemiologic studies, which have found that high levels of circulating IGF-I and low levels of IGFBP-3 are associated with increased risk of several common cancers, including those of the prostate, breast, colorectum, and lung. Evidence further suggests that certain lifestyles, such as one involving a high-energy diet, may increase IGF-I levels, a finding that is supported by animal experiments indicating that IGFs may abolish the inhibitory effect of energy restriction on cancer growth. Further investigation of the role of IGFs in linking high energy intake, increased cell proliferation, suppression of apoptosis, and increased cancer risk may provide new insights into the etiology of cancer and lead to new strategies for cancer prevention. [J Natl Cancer Inst 2000;92:1472–89]

It has been hypothesized that cells with accelerated rates of division and proliferation are predisposed to the development of cancer *(1).* Recently, a number of epidemiologic studies have shown consistently that high circulating levels of a potent mitogen, insulin-like growth factor (IGF)-I, are associated with increased risk for several common cancers, including those of the breast *(2),* prostate *(3),* lung *(4),* and colorectum *(5).* The level of IGF-binding protein (IGFBP)-3, a major IGF-I-binding protein in serum that, in most situations, suppresses the mitogenic action of IGF-I, is inversely associated with the risk of these cancers.

Functionally, IGF-I not only stimulates cell proliferation but also inhibits apoptosis. It has now been recognized that the combination of these mitogenic and antiapoptotic effects has a profound impact on tumor growth *(6).* Besides their direct effect on cancer-related cellular activities, members of the IGF family also interact with a variety of molecules that are critically involved in cancer development and progression, including the sex steroid hormones, products of tumor suppressor genes, and other growth factors. Furthermore, the expression and production of IGF-I, a key peptide hormone that is involved in regulating human growth and development, are influenced by nutrition and physical activity. These features of the IGF family underscore its potential importance in the mechanisms that underlie the roles of lifestyle and behavior in influencing cancer risk.

Several extensive reviews *(7–19)* have addressed the molecular structure and physiologic function of members of the IGF family. Here, we review briefly the molecular and biochemical aspects of each member of the IGF family and the experimental evidence for the role of IGFs in cancer, discuss the potential impact of lifestyle factors on this group of growth factors, and summarize the findings of clinical and epidemiologic studies of the IGF family in relation to cancer etiology and pathogenesis. Collectively, the evidence reviewed here provides insights into the role of mitogenic growth factors in carcinogenesis. All information used in this review was identified by searching the English-language literature in the MEDLINE® database.

THE IGF FAMILY

Overview

IGFs play an important role in regulating cell proliferation, differentiation, apoptosis, and transformation *(11).* IGFs exert their actions by interacting with a specific receptor on the cell membrane, namely, the IGF-I receptor (IGF-IR), and the interaction is regulated by a group of specific binding proteins. All of these molecules are considered to be members of the IGF family, which includes the polypeptide ligands IGF-I and IGF-II, two types of cell membrane receptors (i.e., IGF-IR and IGF-IIR), and six binding proteins (i.e., IGFBP-1 through IGFBP-6). In addition, a large group of IGFBP proteases hydrolyzes IGFBPs, resulting in the release of bound IGFs that then resume their ability to interact with IGF-IR. Thus, as far as IGF action is concerned, IGFBP proteases may also be regarded as part of the IGF family because they indirectly regulate the action of IGFs.

Insulin-Like Growth Factors

IGF-I and IGF-II are single-chain polypeptides *(8,9).* The two molecules have 62% homology in their amino acid sequences. The molecules share additional structural similarities, and their structures resemble the structure of proinsulin. The IGF-I gene is located on chromosome 12 *(8,9),* and the IGF-II gene is located

Affiliations of authors: H. Yu, Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, Shreveport; T. Rohan, Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY.

Correspondence to: Herbert Yu, M.D., Ph.D., Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130-3932 (e-mail: hyu@lsumc.edu).

See "Notes" following "References."

on chromosome 11, 1.4 kilobases (kb) downstream from the insulin gene *(20).* Table 1 summarizes some features of IGF molecules and of their encoding genes.

The IGF-I gene has two promoter sites *(21,22),* and the IGF-II gene has four promoters, i.e., P1–P4 *(23).* Multiple transcripts (i.e., messenger RNAs) for both IGFs have been identified *(8,9).* Initiation of transcription at different promoter sites and alternative splicing are believed to be responsible for producing the multiple transcripts *(23–30).* The presence of distinct transcripts is usually indicative of diverse responses of cells to different environmental stimuli, and animal studies *(31,32)* have suggested that diet and nutrition may induce different patterns of IGF-I transcription.

In adult tissues, IGF-II transcription is initiated from the P1 promoter. Transcription from promoters P3 and P4 is often seen in fetal tissues *(33),* and increased transcription from these promoter sites has been observed in certain cancer tissues *(33–39).* Another feature of IGF-II gene transcription is genomic imprinting, in which the expression of a gene is associated with a particular parental allele *(40,41).* DNA methylation *(42),* histone acetylation *(43),* and use of specific promoter sites *(44,45)* are mechanisms that may control allele-specific transcription. Loss of genomic imprinting in the IGF-II gene is often found in cancer *(46–50).*

Expression of the IGF-I gene is regulated primarily by growth hormone (GH). GH, however, has no regulatory effect on IGF-II expression *(11),* and the primary regulator of IGF-II gene transcription remains unclear. Nevertheless, expression of IGFs is also influenced by various hormones, including estrogens, adrenocorticotropic hormone, thyrotropin, luteinizing hormone, follicle-stimulating hormone (FSH), and human chorionic gonadotropin, as well as by other growth factors, such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF). Diet and nutrition affect circulating IGF-I levels, suggesting a possible impact on IGF-I production *(7,8).*

IGF-I has both immediate and long-term effects on various cellular activities, and these effects are mediated mainly through IGF-IR (*see* next section). IGF-I exerts an acute anabolic action on protein and carbohydrate metabolism by increasing cellular uptake of amino acids and glucose and by stimulating glycogen and protein synthesis *(11).* IGF-I also has a long-term impact on cell proliferation, differentiation, and apoptosis *(11).* IGF-I is a potent mitogen for a wide variety of cells and exerts its mitogenic action by increasing DNA synthesis and by stimulating the expression of cyclin D1, which accelerates progression of the cell cycle from G_1 to S phase *(51,52).* The mitogenic effect of IGF-I can be abolished by suppressing the expression of cyclin D1 *(53).* In addition to stimulating cell cycle progression, IGF-I also inhibits apoptosis. IGF-I is able to stimulate the expression of Bcl proteins and to suppress expression of Bax, which results in an increase in the relative amount of the Bcl/Bax heterodimer, thereby blocking initiation of the apoptotic pathway *(54–56).*

Like IGF-I, IGF-II has mitogenic and antiapoptotic actions and regulates cell proliferation and differentiation. Concentrations of IGF-II in the blood are higher than those of IGF-I in humans of all ages. In adults, IGF-II levels vary between 400 and 600 ng/mL, whereas IGF-I levels range between 100 and 200 ng/mL. Despite its presence at higher concentration in the circulation, IGF-II is believed to play a less important role in postnatal growth than does IGF-I. This conclusion is based on the impact of these IGFs on body growth, their regulation by GH, and their relative binding affinities to IGF-IR and IGFBPs. Animal experiments indicate that the action of IGF-II on body development and growth occurs at a much earlier stage of life than that of IGF-I. Evidence *(57,58)* suggests that IGF-II may play a key regulatory role during embryonic and fetal growth. After birth, the role of IGF-II is gradually replaced by that of IGF-I *(7,11,13).* Levels of circulating IGF-I change substantially with age—they increase slowly from birth to puberty, surge at puberty, and decline with age thereafter—and these changes are regulated by GH. For IGF-II, however, the circulating levels are relatively stable after puberty, and GH has little influence on them. The actions of both IGF-I and IGF-II are mediated through IGF-IR. IGF-I has a twofold to 15-fold higher binding affinity to IGF-IR than does IGF-II *(11).* Three of the six IGFBPs have higher affinity to IGF-II than to IGF-I, and the rest have similar binding affinity to both IGFs *(14).* The combination of high affinity to the receptor and low affinity to the binding proteins results in more IGF-I than IGF-II interacting with IGF-IR.

IGF Receptors

Both IGF-IR and IGF-IIR are glycoproteins and are located on the cell membrane. The two receptors, however, differ completely in structure and function *(12,13).* IGF-IR is a tetramer of two identical α-subunits and two identical β-subunits *(12,13,15).* Structurally, IGF-IR resembles the insulin receptor, and there is

Table 1. Molecular features of members of the insulin-like growth factor family*

	Molecular weight, kd	No. of amino acids	Gene location	Gene size, kb	No. of exons
IGF-I	7.7	70	12q22–12q24	100	6
IGF-II	7.5	67	11p15	30	9
IGF-IR†	225	α-subunit: 706 β-subunit: 626	15q25–15q26	100	21
IGF-IIR	270	2450	6q25–6q27	140	Unknown
IGFBP-1	25.3	234	7p12–7p14	5.2	4
IGFBP-2	31.4	289	2q31–2q34	32	4
IGFBP-3	28.7	264	7p12–7p14	8.9	5
IGFBP-4	26.0	237	17q12–17q21	12	4
IGFBP-5	28.6	252	2q31–2q24	33	4
IGFBP-6	22.8	216	12q13	4.7	4

*__Abbreviations used:__ IGF = insulin-like growth factor; IGFBP = insulin-like growth factor-binding protein; IGF-IR = IGF-I receptor; IGR-IIR = IGF-II receptor; kb = kilobases; kd = kilodaltons.

†IGF-IR is a tetrameric protein (two α- and two β-subunits).

60% homology between them. IGFs and insulin are able to cross-bind to each other's receptor, albeit with much weaker binding affinity than that for the preferred ligand *(59,60).* A hybrid receptor that is composed of one α-subunit and one β-subunit of IGF-IR and one α-subunit and one β-subunit of the insulin receptor *(11,12)* has been identified. The amount of insulin/IGF-I hybrid receptor varies substantially from tissue to tissue. Since its binding affinity for IGF-I is higher than that for insulin, the receptor is thought to function predominantly as an IGF-I receptor, but its biologic importance remains largely unknown.

IGF-IIR is monomeric *(13,16,61,62).* Three ligand-binding regions are found in the extracellular domain of the receptor, one for IGF-II binding and two for proteins containing mannose-6-phosphate (M6P), including renin, proliferin, thyroglobulin, and the latent form of transforming growth factor (TGF)-β *(11).* Binding of IGF-IIR to TGF-β activates the latter *(16,63).* Since IGF-IIR can bind both IGF-II and M6P-containing molecules, it is also called the IGF-II/M6P receptor.

The expression of IGF-IR is regulated by steroid hormones and growth factors *(13,15).* Since high IGF-I levels result in a decline in IGF-IR, IGFs may act as negative feedback signals to repress expression of IGF-IR *(64,65).* In contrast to the effect of IGFs, other growth factors, including basic FGF, PDGF, and EGF, stimulate IGF-IR expression *(15,66,67).* The expression of IGF-IR is also stimulated by estrogens, glucocorticoids, GH, FSH, luteinizing hormone, and thyroid hormones *(12,15).* On the other hand, tumor suppressor gene products, such as wild-type p53 protein and WT1 (Wilms' tumor protein), inhibit expression of IGF-IR *(68–71).* Nutrition also affects IGF-IR levels *(72–74).* Little is known about the regulation of IGF-IIR expression, although some studies *(11,13,75,76)* have suggested that insulin, IGFs, EGF, and M6P may increase the level of IGF-IIR in the cell membrane.

Binding of IGFs to IGF-IR activates the receptor's tyrosine kinase activity, which triggers a cascade of reactions among a number of molecules involved in the signal transduction pathway. Two distinct signal transduction pathways have been identified for IGF-IR. One pathway activates Ras protein, Raf protein, and mitogen-activated protein kinase, and the other pathway involves phosphoinositol-3-kinase *(11,12).* Other signal transduction pathways that are initiated by IGF-IR may also exist *(77).* Activation of IGF-IR by ligand binding is necessary to allow IGF-IR to mediate the actions of IGFs. In addition to mediating the mitogenic and antiapoptotic actions of IGFs, IGF-IR is involved in cell transformation. *In vitro* experiments *(78)* have shown that removal of IGF-IR from the cell membrane by eliminating the IGF-IR gene, by suppressing its expression, or by inhibiting its function can abolish cell transformation.

IGF-IIR has no tyrosine kinase activity, and it binds only to IGF-II *(16).* Since binding of IGF-IIR to IGF-II results in degradation of IGF-II, IGF-IIR acts like an antagonist to IGF-II, reducing its biologic activity *(16).* Because of this effect, IGF-IIR has been considered to be a potential tumor suppressor molecule. A unique feature of IGF-IIR may contribute to its ability to act as a scavenger for circulating IGF-II. Upon proteolytic cleavage, the extracellular domain of the receptor is disassociated from the cell membrane as a soluble fragment that circulates in the blood with the ability to bind to IGF-II and to facilitate its degradation *(79–84).*

IGF-Binding Proteins

Six IGFBPs with specific binding affinities for IGFs have been identified. These proteins have some structural homology *(13,14,85–90).* Table 1 summarizes the molecular features of these proteins. IGFBPs undergo substantial post-translational modification, which affects their binding affinities for IGFs *(17,18,85).* IGFBPs are able to bind to specific cell membrane receptors as well as to attach to the cell surface or to the extracellular matrix *(17,19,85).*

Regulation of IGFBP gene transcription is complex and tissue specific. A number of hormones, including estrogens, glucocorticoids, parathyroid hormone, FSH, GH, thyroid hormone, insulin, vitamin D, and cortisol, have been found to regulate the expression of IGFBPs *(17,19,91–96).* Growth factors, including FGF, EGF, TGF-β, PDGF, and IGFs themselves, as well as retinoic acid, are also involved in the regulation of expression of these binding proteins *(96–101).* The expression of IGFBP-1 is suppressed by insulin and IGFs *(17,19,91).* As with its role in the regulation of IGFs, GH plays an important role in stimulating the expression of IGFBP-3 *(92).* Certain cytokines, such as interleukin 1 and tumor necrosis factor-α, are also able to increase IGFBP-3 levels *(102).*

IGFBPs have multiple and complex functions, which can be either IGF dependent or IGF independent. With respect to IGF-dependent function, IGFBPs are able to inhibit or to enhance the action of IGFs, resulting in either suppression or stimulation of cell proliferation *(17,19).* These opposing effects of IGFBPs on IGFs are determined by the molecular structures of the binding proteins. When binding to IGFs, IGFBPs play three major roles: 1) transporting IGFs, 2) protecting IGFs from degradation, and 3) regulating the interaction between IGFs and IGF-IR. Normally, IGFBPs have higher binding affinity to IGFs than does IGF-IR; therefore, binding of IGFBPs to IGFs blocks the interaction between IGFs and IGF-IR and suppresses IGF action *(17,19).* However, binding of IGFBPs to IGFs also protects IGFs from proteolytic degradation, and that protection can enhance the action of IGFs by increasing their bioavailability in local tissue *(17,19).* The actual impact of IGFBPs on IGFs depends largely on post-translational modification of IGFBPs by phosphorylation and proteolysis *(17–19,103–105).* The association of IGFBPs with the cell membrane or extracellular matrix may also affect the binding affinity of IGFBPs to IGFs.

IGFBP-1, IGFBP-2, IGFBP-3, and IGFBP-5 have been found to have dual regulatory effects on IGFs, either suppressing or enhancing the action of IGFs. The effects of IGFBP-2, IGFBP-3, and IGFBP-5 on IGFs are regulated by proteolysis of the binding proteins, whereas the effect of IGFBP-1 on IGFs is affected by phosphorylation *(11,17–19).* In addition to undergoing proteolysis and phosphorylation, IGFBP-1, IGFBP-2, IGFBP-3, and IGFBP-5 bind to specific cell membrane receptors or attach to the cell surface, which reduces their binding affinities for IGFs and results in the release of free IGFs *(11,17–19).* The binding affinity of IGFBP-5 for IGFs also decreases when IGFBP-5 is associated with extracellular matrix *(17,18).* IGFBP-1, IGFBP-2, and IGFBP-5 are all suspected of having IGF-independent effects on cellular activities, such as cell adhesion and migration *(11,17,19).*

IGFBP-3 is found not only to regulate the mitogenic action of IGFs but also to inhibit their antiapoptotic effect *(106).* Besides its IGF-dependent function, IGFBP-3 also has an IGF-independent inhibitory effect on cell growth *(17,19).* This effect

may be mediated through a cell membrane receptor that is specific for IGFBP-3 *(107,108).*

IGFBP-4 and IGFBP-6 are able to inhibit the mitogenic action of IGFs, but these proteins, unlike the others, do not enhance the actions of IGFs *(11,19).* IGFBP-4 and IGFBP-6 also undergo proteolysis, but this change seems to have little impact on their functions *(11,17,109,110).*

IGFBP Proteases

Since the actions of IGFs can be either suppressed or enhanced by IGFBPs, proteolysis of IGFBPs by IGFBP proteases is an important factor in determining the regulatory impact of IGFBPs on IGF action. Prostate-specific antigen (PSA), a serine protease, is able to cleave IGFBP-3 and IGFBP-5 *(19,111),* and proteolysis of IGFBP-3 by PSA reduces its binding affinity to IGF-I, which restores the mitogenic activity of IGF-I *(112).* Another serine protease, γ-nerve growth factor, has 65% homology to PSA and proteolytic activity toward IGFBP-4 and IGFBP-6 *(109).* Cathepsin D, an acid-activated lysosomal protease, can proteolyze all six IGFBPs *(103,110,113).* Matrix metalloproteinases, including interstitial collagenase, gelatinase A, stromelysin 1, gelatinase B, and disintegrin metalloproteinase, are involved in the proteolysis of IGFBP-2, IGFBP-3, IGFBP-4, and IGFBP-5 *(19,114–116).* Other proteolytic enzymes that are able to hydrolyze IGFBPs include plasmin, thrombin, and pregnancy-associated plasma protein-A *(117–119).*

Regulation of IGFBP proteolysis is complex and remains poorly understood. Changes in physiologic condition can influence the proteolysis of IGFBPs in the circulation. For example, serum from pregnant women has higher IGFBP proteolytic activity than serum from nonpregnant women *(120).* The expression or presence of one binding protein affects the proteolysis of the others *(121,122).* Binding between IGFBPs and IGFs also affects IGFBP proteolysis *(17).* It has also been shown that IGFs modulate the proteolytic activities of IGFBPs, suggesting that IGFs have an autocrine regulatory loop to control their own action *(123).* Insulin influences the activities of IGFBP proteases *(124,125),* but GH has little impact on these proteases *(126).* Estrogens may regulate the proteolysis of IGFBPs *(127).*

IGFs and Cancer: Experimental Evidence

The possible involvement of IGFs in cancer was observed initially in cell culture experiments *(128). In vitro* studies have shown consistently that members of the IGF family not only regulate the growth of various cancer cells but also interact with other cancer-related molecules. Animal experiments have suggested further that IGFs may mediate the effect of energy intake on the risk of cancer.

Direct Involvement in Cancer

IGF-I and IGF-II are strong mitogens for a wide variety of cancer cell lines, including sarcoma, leukemia, and cancers of the prostate, breast, lung, colon, stomach, esophagus, liver, pancreas, kidney, thyroid, brain, ovary, and uterus (both cervical and endometrial) *(128–133).* IGFs are also overexpressed in certain cancers *(128).* Animal experiments *(134,135)* indicate that overexpression of IGF-I increases the likelihood of tumor development in certain tissues. Overexpression of IGF-II may result from loss of genomic imprinting in IGF-II, loss of function of a transcriptional repressor, or change of transcription promoter sites *(130,136–138).* Cancer cells with a strong tendency to metastasize have higher expression of IGF-II and IGF-IR than those with a low ability to do so *(139).* The strong impact of IGF-II on cancer growth that is observed consistently in laboratory studies and the paucity of clinical and epidemiologic studies that have found an association between circulating IGF-II and cancer risk suggest that IGF-II may exert its action via paracrine rather than endocrine regulation.

The effects of IGFs on cancer cells are mediated through IGF-IR. Eliminating IGF-IR from the cell membrane, blocking the interaction of IGFs with IGF-IR, or interrupting the signal transduction pathway of IGF-IR can abolish the mitogenic action of IGFs on cancer cells *(130,140–142).* IGF-IR also plays a critical role in cell transformation that is induced by tumor-virus proteins and oncogene products. IGF-IR is involved not only in the induction of cell transformation but also in the maintenance of the transformed phenotype *(130).* IGF-IR is overexpressed in certain cancers, and its overexpression is associated with aggressive tumors *(143,144).* The hybrid receptor that binds both IGF-IR and insulin may also mediate the effect of IGFs on cancer *(145,146).* A recent study *(147)* indicates that the insulin receptor is involved in mediating the actions of IGF-II on breast cancer.

Since IGF-IIR antagonizes the effect of IGF-II, loss of IGF-IIR function is expected in cancer. One study found cancer-related missense mutations in the IGF-IIR gene with resultant disruption of the binding of IGF-IIR to its ligand. Cancer cells that lack the ability to degrade IGF-II have been shown to have a strong growth potency *(148).* Suppressing the expression of IGF-IIR yields the same effect as mutation in the IGF-IIR gene *(149).* Reestablishing the function of IGF-IIR in cancer cells that lack IGF-IIR reduces cancer growth and increases apoptosis *(150).*

In cancer, IGFBPs regulate the action of IGFs *(151–156).* In most situations, the binding proteins suppress the mitogenic action of IGFs and promote apoptosis *(157–159).* However, because of the presence of IGFBP proteases *(17–19,160),* two *in vitro* studies *(161,162)* have found that IGFBPs are able to stimulate the growth of cancer cells. Oh et al. *(107)* found that IGFBP-3 inhibited breast cancer cell growth without interacting with IGFs. Other studies *(163,164)* reported that IGFBP-3 could induce apoptosis of breast and prostate cancer cells without the presence of IGFs or IGF-IR.

Interactions With Other Molecules

Many molecules that are known to be involved in cancer have been found to have substantial interactions with members of the IGF family. In general, IGFs interact synergistically with other mitogenic growth factors and steroids and antagonize the effects of antiproliferative molecules in cancer cells.

In breast cancer cells, estrogens enhance the mitogenic effect of IGF-I, induce expression of IGF-I, and stimulate production of IGF-IR *(165–168).* Estrogens also repress synthesis of some IGFBPs in breast tissue *(169,170).* In breast cancer cells, estrogens decrease the expression of IGF-IIR and increase the level of IGFBP proteases *(171).* The interaction between estrogens and IGF is reciprocal. IGF-I enhances expression of estrogen receptor (ER) in breast cancer cells, and ER levels in breast tissue are associated with the levels of some IGFBPs *(172,173)* (*see* "Cancer Prognosis" section *below*).

Antiestrogenic agents increase the expression of IGFBPs *(174–176).* Tamoxifen, which is antiestrogenic in breast tissue,

abolishes the effects of estrogens on IGF-I, inhibits transcription of IGF-I, and attenuates the response of IGF-IR to IGFs *(177,178)*

The expression of IGFs in the uterus is regulated by estrogens, and IGFBPs interfere with this process *(179–181)*. Since tamoxifen has estrogenic effects in the uterus, synergistic interplay between tamoxifen and IGFs is also observed in endometrial cells. Tamoxifen enhances the IGF-stimulated growth of endometrial cancer cells *(182)*. Furthermore, there is an interaction between the signal transduction pathways of the two systems. IGF-I can enhance ER-induced gene transcription in the absence of estrogen *(183)*. IGFBPs, in contrast, suppress the transcriptional activation that is initiated by ERs *(184)*. IGFs increase the activity of estrone sulfatase, which hydrolyzes estrone sulfate to estrone *(185)*.

Synergistic interaction is also observed between IGFs and EGF, another potent mitogen. In cervical cancer cells, EGF is able to stimulate IGF-II expression and to increase IGF-IR's response to its ligand. Increases in IGF levels, in turn, enhance the mitogenic action of EGF *(186,187)*. In addition, EGF can suppress the expression of IGFBP-3 and increase the availability of free IGFs, further enhancing the mitogenic signal of IGFs *(188)*. In prostate cancer cells, interrupting the signaling pathway for EGF suppresses not only the effect of EGF but also that of IGF-I *(189)*.

Several studies have suggested that IGFs may mediate the effects of tumor viruses. In hepatocellular carcinoma, hepatitis B virus stimulates IGF-IR expression *(190)* and increases transcription of the IGF-II gene from the P3 and P4 promoters *(191)*. Hepatitis C virus may also be responsible for increased IGF-II transcription from fetal promoters in hepatitis C virus-related liver disease, including hepatocellular carcinoma *(192)*.

Several antiproliferative molecules exert their actions by interfering with IGF signaling. Inhibition of breast cancer cell growth by TGF-β is mediated through induction of IGFBP-3, which inhibits the mitogenic action of IGFs *(98,193)*. Like TGF-β, retinoic acid inhibits the growth of breast cancer cells by increasing IGFBP-3 expression *(97,101,109)*. Vitamin D and its synthetic analogues can suppress the stimulatory effect of IGFs on the growth of breast and prostate cancer cells by increasing the expression of IGFBPs and reducing the expression of IGF-IR and IGF-II *(94,95,194,195)*.

Tumor suppressor gene products have a profound impact on the IGF family. Wild-type p53 protein induces the expression of IGFBP-3 *(196)*, represses the transcription of IGF-II from its P3 and P4 promoters *(33,197)*, and suppresses IGF-IR expression *(70,198,199)*. Not only does p53 regulate the action of IGFs but also IGFs influence p53 function. When IGF-I-induced DNA synthesis takes place in breast cancer cells, p53 loses its function by undergoing phosphorylation and relocation from the nucleus to the cytoplasm *(200)*. Other tumor suppressor proteins that interact with IGFs include the Wilms' tumor suppressor gene product WT1 *(69,201,202)*, the mammary-derived growth inhibitor MDGI *(203)*, and the tumor suppressor gene PTEN *(204)*.

Energy Intake

Animal experiments have shown that energy restriction can reduce the risk of cancer and inhibit tumor growth *(205–208)* and that this effect can be attributed in part to IGFs *(209,210)*. Restriction of energy intake in rats transplanted with human prostate cancer cells slows the growth of cancer and accelerates apoptosis. These effects are associated with a decrease in circulating IGF-I *(209)*. Dietary restriction reduces the growth rate of bladder cancer in mice *(210)*. When diet-restricted mice are supplemented with IGF-I, the effect of dietary restriction on cancer growth disappears, and the tumors in these animals grow at the same rate as those in animals that are not on food restriction, suggesting that the effect of energy restriction on cancer is mediated mainly through IGF-I *(210)*.

Circulating IGFs and IGFBPs and Their Determinants

IGFs in Blood

More than 90% of IGFs in the circulation are bound to the IGFBPs, mainly IGFBP-3. The complex of IGFBP-3 and IGFs is further bound to another protein, which is called acid-labile subunit and is a glycoprotein with a molecular mass of about 63 kd *(211)*. These three-molecule complexes are the major circulating forms of IGFs in the blood. All IGFs and IGFBPs are detectable in the blood *(7,14)*, but measurement of serum or plasma IGF levels must be preceded by a procedure that separates IGFs from their binding proteins *(212)*. Without the separation step, IGF-I measured in the blood is believed to represent only free IGF-I, which is about 1% of the total IGF-I in the circulation *(213)*.

Although there is considerable interindividual variation in serum and plasma levels of IGFs and IGFBPs, blood levels of IGFs in each individual are relatively constant, and there is no apparent diurnal or circadian variation *(7)*. Besides age, the determinants of this variation remain largely unknown, although the relationship of these growth factors, in particular that of IGF-I, with dietary factors and lifestyle has been investigated in a number of studies *(2,3,5,214–237)*.

Similar to levels of IGFs, levels of most of the IGFBPs are also quite stable in the circulation, with the exception of those of IGFBP-1. Because of its close relationship with insulin, serum IGFBP-1 levels decrease in response to increased levels of insulin after food intake *(238)*. Nutritional status also affects the level of IGFBP-2 in the serum. Fasting increases its level substantially; however, this response occurs slowly. A role for insulin in regulating the level of IGFBP-2 in serum has been suggested by animal experiments but has not been seen in humans *(11)*.

Effects of Age and Sex

Levels of IGFs and IGFBPs in the blood show little variation with sex but vary substantially with age. Serum IGF-I level is low at birth and increases gradually until puberty *(239–244)*. The rate of increase undergoes a sharp upsurge at puberty, after which the concentration declines slowly with age. Serum IGF-II levels also increase with age from birth to puberty, but after puberty they remain stable *(239,240)*. Concentrations of IGFBP-1 and IGFBP-2 in blood are high at birth and decline with age until puberty *(240,241)*. After that, the levels of these proteins remain relatively constant or increase slightly. The age-specific distributions for IGFBP-3 and acid-labile subunit are similar to the distribution for IGF-I *(240,242,243)*. Limited data suggest that serum IGFBP-5 level declines with age, whereas IGFBP-4 and IGFBP-6 concentrations increase with age *(240,244)*.

Diet, Nutrition, Anthropometric Characteristics, and Physical Activity

Energy intake, body mass index ([weight in kg]/[height in m]^2), and physical activity all appear to affect blood levels of IGFs and IGFBPs. However, the intimate relationship among these variables makes disentanglement of their independent effects difficult. Four studies *(3,5,220,223)* found no association between the level of IGF-I and height. Of studies that investigated the association between IGF-I and body mass index, some showed no association with total IGF-I *(3,5,215,220,223,225),* whereas others showed inverse associations either with total *(217,222)* or with free *(225)* IGF-I.

Nutritional status and dietary energy intake are critical regulators of IGF-I level, and the IGF family links nutrition to growth *(72).* IGF-I levels are decreased in association with protein-calorie malnutrition, and they increase in response to improvements in energy intake *(226).* Fasting also results in a decrease in IGF-I level *(227),* but the effect is smaller in obese subjects who are presumably less dependent on energy intake to maintain IGF-I levels *(228).* Overnutrition has an effect that is opposite that of fasting, in that it results in an increase in IGF-I level *(229).* Studies of normal adults have demonstrated a positive correlation between protein intake and serum IGF-I levels *(245).* A 50% reduction in calorie intake or a 30% reduction in protein intake has been shown to result in a decline in serum IGF-I and IGFBP-3 levels and an increase in IGFBP-2 level *(246).* These findings are consistent with those of animal experiments *(247–251),* which have also shown that restriction of nutrients has diverse effects on IGF-I gene transcription *(252).* Although all of these studies demonstrate a substantial impact of energy and protein intake on the IGF family, the exact nature of the dose–response relationships between food intake and levels of IGFs in circulation remains to be determined.

The association between IGF-I level and physical activity appears to be rather complex, and current evidence does not allow clear conclusions to be drawn. Cross-sectional studies have shown either no association between physical activity and IGF-I levels *(5,220,223,230)* or positive associations with leisure-time exercise *(214),* general physical activity *(224),* or physical fitness *(215)* and training *(232).* A nonrandomized study *(231)* that involved a 16-week training program did not produce a change in IGF-I levels. Some randomized trials have shown that IGF-I levels increase in association with a 2-week training intervention *(233)* or a strength test *(234),* but others *(235,236,253)* have shown that IGF-I decreases after a 5-week period of endurance training in adolescents. One study *(234)* found no association of IGF-I level with strength training. The inconsistent findings for IGF levels in relation to physical activity may be age related. Exercise increases IGF-I levels in adults *(233,234);* however, in children and adolescents, the opposite effect is observed *(72,235,236).*

Since many tissues are able to express the IGF-I gene, the effect of IGF-I is subject to both endocrine and paracrine regulations. Most circulating IGFs and IGFBP-3 are manufactured in the liver. Levels of IGF-I in circulation are closely associated with body growth, especially at puberty. Children with short stature have low circulating IGF-I levels *(254,255),* and individuals with acromegaly have elevated serum IGF-I levels *(256,257).*

The assumption that IGF-I exerts its action on body growth mainly through endocrine regulation was challenged recently. Two animal studies *(258,259)* suggested that hepatic IGF-I was not involved in growth regulation. However, these findings are controversial, since paracrine regulation of IGF-I may have been elevated to compensate for the loss of endocrine-regulated IGF-I, and the action of IGF-II was not evaluated or controlled in the experiment.

Effect of Alcohol Consumption and Cigarette Smoking

The relationship is unclear between alcohol consumption and IGF levels. Different levels of alcohol consumption may have opposite effects on IGF levels *(5,223,260–262).* Long-term and heavy consumption of alcohol can cause severe damage to liver function, and loss of liver function may result in a decline in the production of IGFs *(260).* Indeed, it has been shown that alcoholics have relatively low IGF-I levels *(220).* But some laboratory experiments have shown that alcohol enhances IGF-I action and expression *(261,262).* One cross-sectional study *(223)* found a positive association between moderate alcohol consumption in elderly women and serum IGF-I levels, but the opposite relationship was observed in another study *(5).*

Different associations between IGF levels and cigarette smoking have been reported. Two studies *(223,263)* found a positive association between serum levels of IGF-I and cigarette smoking, but one study *(220)* observed an inverse association and two studies *(4,5)* showed no association. The level of IGFBP-3 was found to be inversely associated with smoking in one study *(263).* These associations might have been confounded by the association between alcohol consumption and cigarette smoking.

IGFs and Cancer: Clinical and Epidemiologic Evidence

Clinical Studies

In a number of clinical studies, levels of IGFs, IGF-IR, and IGFBPs were compared in subjects with and without cancer *(264–274).* IGF-I levels have been shown to be higher in the plasma and serum of women with breast cancer than in comparable specimens from women without the disease *(264,266,274),* although other studies have shown no difference between case and control subjects with respect to levels of IGF-I *(267,268)* or IGF-II *(268)* in the serum. One study *(268)* showed lower serum levels of IGFBP-1, IGFBP-3, and IGFBP-6 in case subjects as compared with control subjects, but another study *(267)* found no difference. A 10-fold increase in IGF-IR content (measured as nanograms per milligram of protein) has been observed in breast cancer tissue as compared with normal tissue *(265).*

Two studies of colon cancer *(269,270)* found similar levels of IGF-I in the sera of case and control subjects, whereas one study *(270)* reported higher levels of IGF-II, IGFBP-2, and IGFBP-3 in case subjects as compared with control subjects. In endometrial cancer, one study *(271)* found lower serum IGF-I levels in case subjects as compared with control subjects but no difference in IGFBP-1 levels between the two groups. A study with postmenopausal endometrial cancer patients *(272)* showed higher serum IGF-I levels, lower IGFBP-1 levels, and no difference in IGFBP-3 levels when compared with healthy control subjects. Another study *(275)* reported low IGF-I gene transcription in endometrial cancer tissue but no difference in the production of IGF-I and IGF-IR.

Clinical studies have found higher levels of serum IGF-I in prostate cancer patients than in control subjects *(276,277)* and higher levels of serum IGFBP-2 in prostate cancer patients than in patients with benign prostatic hyperplasia or in healthy control subjects *(273,278,279).* The transcription and production of IGFBP-2 are also higher in prostate cancer tissue than in normal tissue *(280).* IGFBP-3 levels have been shown to be low in the serum *(279)* and tumor tissue *(280)* of prostate cancer patients. Studies *(281,282)* also suggest increased expression of IGF-II, IGFBP-4, and IGFBP-5 in prostate cancer tissue.

Differences in levels of some IGFBPs in ovarian cancer patients as compared with those of control subjects are similar to those of prostate cancer patients. Higher levels of IGFBP-2 and lower levels of IGFBP-3 have been observed in sera of patients with epithelial ovarian cancer as compared with normal control subjects *(283,284).* Elevated IGFBP-2 expression has also been found in ovarian tumor tissue *(283,285).* Studies *(283,286)* further suggest that IGF-I levels may be increased in the serum and cancer tissue of patients with ovarian cancer.

In general, the clinical studies reviewed here have been relatively small, have not included adjustment for potential confounding factors, have not always described clearly the source of the study subjects (in particular, the source of the comparison groups), and have not presented estimates of cancer risk in association with IGF levels. Although the inconsistencies in the patterns described above do not allow firm conclusions to be drawn, the clinical data suggest that the IGFs have a role in cancer development.

Epidemiologic Studies

Epidemiologic studies *(2–5,237,287–296)* have investigated the role of IGFs and IGFBPs in the etiology of cancers of the breast, colon and rectum, prostate, and lung and of childhood leukemia (Table 2). Although some of these studies were relatively small, most were characterized by careful definition of the comparison groups, adjustment for covariates, and estimation of cancer risk by levels of the IGF or IGFBP of interest. To date, most studies have focused on cancer risk in association with serum or plasma levels of IGF-I, IGF-II, and IGFBP-3, or combinations thereof, and they have provided reasonably consistent support for increased risk of solid tumors in association with relatively high levels of IGF-I, decreased risk of solid tumors and of childhood leukemia in association with relatively high levels of IGFBP-3, and increased risk of breast cancer in association with a high ratio of IGF-I to IGFBP-3. For breast cancer, the findings appear to hold largely for premenopausal women. Mutual adjustment of IGF-I and IGFBP-3 levels appears to strengthen the association of each of these factors with cancer risk.

A high IGFBP-3 level is generally associated with a reduced risk of cancer. However, two case–control studies, one of breast cancer *(288)* and the other of prostate cancer *(295),* suggested that risk was increased in association with relatively high levels of IGFBP-3 (but the findings were not statistically significant). The two studies *(3,4)* that examined cancer risk in association with IGF-II level showed no association, as did one study *(288)* that examined risk in association with IGFBP-1 level. A recent study *(296),* however, found that high levels of IGFBP-1 in serum were associated with increased risk of prostate cancer.

Most of the currently available data are from case–control studies. Unless they are nested within prospective investigations, case–control studies are generally unable to establish the temporal nature of an association due to possible effects of the disease process on blood levels of the molecules of interest and are potentially susceptible to selection and information biases *(293).* The results of case–control studies with respect to IGF levels and the risk of breast, prostate, and colorectal cancers are substantially—but not completely—in accord with those of cohort studies at the same sites.

Cancer Prognosis

The association between members of the IGF family and various predictors of cancer prognosis has been investigated in a number of cross-sectional studies *(265–267,297–313).* Prognostic factors that have been examined in relation to IGF levels include age, menopausal status, ER and progesterone receptor (PR) status, tumor size, lymph node involvement, and histologic grade. Several prospective studies *(300–302,307–309,312,313)* have also examined the association of IGF levels with disease-free or overall survival from cancer.

To date, work in this area has focused largely on breast cancer. Many of the investigations have been relatively small, which may have compromised their ability to detect associations. Nevertheless, evidence suggests that IGF-IR is detectable *(265,297–301)* and sometimes amplified *(302)* in tissues that are ER or PR positive, although two studies *(265,274)* showed no association. Findings on whether IGF-IR overexpression in breast cancer affects prognosis are contradictory. Two studies *(314,315)* suggested that IGF-IR expression might lead to poor prognosis, whereas one study *(265)* found that overexpression of IGF-IR is associated with less aggressive lesions. However, studies *(303–306,310–313)* have consistently demonstrated an inverse association between tissue IGFBP-3 levels and ER status. Some *(310–312)* but not all *(306,313)* of the studies have also suggested a similar association for PR status. Clinical studies *(266,267,304–307,309,311)* have not found consistent evidence for associations between IGF levels and age, menopausal status, tumor size, lymph node involvement, or degree of tumor differentiation.

Studies of the association of IGFs with disease-free or overall survival have also focused largely on breast cancer. One study *(300)* found no association between IGF-IR level and disease-free survival, one *(301)* found better disease-free and overall survival in women with IGF-IR-positive tumors after 40 months of follow-up and after adjustment for ER and PR status and other prognostic indicators, and one *(302)* found worse overall survival in those who had evidence of IGF-IR amplification in their tumors. Detection of IGFBP-3 in breast tissue has been reported to have no association with disease-free survival *(312,313)* and to have either no association with overall survival *(312)* or an association with increased risk of death *(313);* the latter association was independent of other prognostic factors *(313).*

In relation to the other IGF markers that have been studied, one study *(307)* showed an association between increased IGFBP-4 levels in breast tissue and decreased overall survival in women with large tumors (>2 cm in diameter), one study *(309)* showed no association of the level of IGF-II in breast tissue with disease-free or overall survival, and one study *(308)* showed no association of IGF-I levels in serum with overall 2-year survival.

With the exception of two studies *(302,313),* the studies described here have been relatively small and have not employed long follow-up periods. Nevertheless, on the basis of the cur-

Table 2. Summary of epidemiologic studies of IGFs, IGFBPs, and cancer risk*

Cancer	Author (reference No.)	Study design	Comparison	RR (95% CI)	Adjusted for
Breast	Bruning et al. *(237)*	Case–control; 150 premenopausal and postmenopausal case subjects (with stage I or stage II disease) and 441 premenopausal and postmenopausal population control subjects	Ratio of serum IGF-I/IGFBP-3: $\geq 56.83 \times 10^{-3}$ versus $<34.58 \times 10^{-3}$	7.34 (1.67–32.16) *P* for trend = .006	Age, menopausal status, family history of breast cancer, premenopausal BMI, WHR, albumin, C-peptide, and testosterone
	Bohlke et al. *(287)*	Case–control; 94 population-based premenopausal case subjects with ductal carcinoma *in situ* and 76 age- and residence-matched control subjects	Plasma IGF-I: >175.5 versus ≤121.5 ng/mL IGFBP-3: >3493.4 versus ≤3239.4 ng/mL High versus low ratio of IGF-I/IGFBP-3†	1.8 (0.7–4.6) 0.7 (0.3–1.7) 1.6 (0.7–3.8)	Age, age at first birth, age at menarche, height, BMI, log estradiol (pg/mL), ethnic group, parity, and first-degree family history of breast cancer; IGF-I and IGFBP-3 mutually adjusted
	Hankinson et al. *(2)*	Cohort of 32 826 women; 397 case patients with *in situ* or invasive breast cancer and 620 control subjects matched on year of birth, time of blood draw, fasting status, and month of blood sampling, menopausal status, and use of postmenopausal hormones	Plasma IGF-I All women: ≥220 versus <110 ng/mL Postmenopausal women: ≥220 versus <110 ng/mL Premenopausal and age <50 y: ≥207 versus <158 ng/mL High versus low ratio of IGF-I/IGFBP-3 in premenopausal women age <50 y†	 1.06 (0.66–1.70)‡ *P* for trend = .51 0.89 (0.51–1.55) *P* for trend = .99 7.28 (2.40–22.0) *P* for trend = .01 2.46 (0.97–6.24)	Matching factors
	Del Giudice et al. *(288)*	Case–control; 99 hospital-based premenopausal case subjects with lymph node-negative invasive breast cancer and 99 control subjects with nonproliferative breast disease	High versus low plasma IGF-I concentration† High versus low plasma IGFBP-1 concentration† High versus low plasma IGFBP-3 concentration†	1.47 (0.66–3.27) 0.98 (0.44–2.18) 2.05 (0.93–4.53)	Age; IGFBP-1 also adjusted for weight
	Agurs-Collins et al. *(289)*	Case–control; 30 postmenopausal African-American case subjects and 30 control subjects	1 ng/mL increase in plasma IGF-I concentration	1.012 (1.002–1.023)	Adjustment factors not specified
Colon and rectum	Ma et al. *(5)*	Cohort of 14 916 men; 193 case subjects and 318 age- and smoking-matched control subjects	Plasma IGF-I: ≥230 versus <135 ng/mL Plasma IGFBP-3: ≥2598 versus <2473 ng/mL	2.51 (1.15–5.46) *P* for trend = .02 0.28 (0.12–0.66) *P* for trend = .005	Age, cigarette smoking, BMI, alcohol intake, and plasma IGF-I or IGFBP-3
	Pollak et al. *(290)*	Case–control; 40 incident colorectal cancer case subjects and 342 control subjects with no history of colon cancer and normal colonoscopy results	90th versus 10th percentile IGF-I/IGFBP-3 IGF-I IGFBP-3	 2.64 (1.07–6.49) 4.96 (1.28–19.19) 0.16 (0.04–0.56)	Age and sex; IGF-I and IGFBP-3 mutually adjusted
	Giovannucci et al. *(291)*	Cohort of 32 826 women; 79 case subjects and an unknown number of control subjects matched on age, time of blood draw, and indication for endoscopy	High versus low plasma IGF-I concentration† High versus low plasma IGFBP-3 concentration†	2.23 (0.91–5.47) 0.25 (0.08–0.79)	IGF-I and IGFBP-3 mutually adjusted
	Manousos et al. *(292)*	Case–control; 41 case subjects and 50 control subjects	High versus low serum IGF-I concentration† High versus low serum IGF-II concentration† High versus low serum IGFBP-3 concentration†	2.3 (0.6–9.1) 2.7 (0.7–10.5) 0.5 (0.1–1.7)	Age, sex, education, height, and BMI; IGFs and IGFBP-3 mutually adjusted
Prostate	Mantzoros et al. *(294)*	Case–control; 52 case subjects and 52 age-matched control subjects	60-ng/mL increase in serum IGF-I	1.91 (1.00–3.73)	Age, height, BMI, education, sex hormone-binding globulin, testosterone, estadiol, dihydrotestosterone, and dehydroepiandrosterone sulfate

(Table continues)

Table 2 (continued). Summary of epidemiologic studies of IGFs, IGFBPs, and cancer risk*

Cancer	Author (reference No.)	Study design	Comparison	RR (95% CI)	Adjusted for
	Chan et al. *(3)*	Cohort of 14 196 men; 152 case subjects and 152 control subjects matched on age, smoking status, and duration of follow-up	Plasma IGF-I: ⩾293.76 versus <184.8 ng/mL High versus low plasma IGF-II† High versus low plasma IGFBP-3†	4.32 (1.76–10.6) *P* for trend = .001 0.97 (0.48–1.95) *P* for trend = .74 0.41 (0.17–1.03) *P* for trend = .09	PSA, height, weight, BMI, androgen receptor CAG polymorphisms, and plasma hormones; IGF-I and IGFBP-3 mutually adjusted
	Wolk et al. *(295)*	Case–control; 224 case subjects and 224 population control subjects frequency matched on age	Serum IGF-I: ⩾177.7 versus <144.7 ng/mL Serum IGFBP-3: ⩾2955 versus <2465 ng/mL	1.43 (0.88–2.33) *P* for trend = .04 1.21 (0.75–1.93) *P* for trend = .10	Age, height, and BMI
	Signorello et al. *(296)*§	Case–control; 208 case subjects and 70 population control subjects frequency matched on age	Serum IGFBP-1: >17 versus ⩽10 ng/mL	5.1 (2.4–10.7)‖	Age, BMI, and height
Lung	Yu et al. *(4)*	Case–control; 204 case subjects and 218 control subjects matched on age, sex, race, and smoking status	Plasma IGF-I: ⩾177.5 versus <98.4 ng/mL Plasma IGF-II: ⩾683.7 versus <250.2 ng/mL Plasma IGFBP-3: ⩾44.4 versus <31.3 ng/mL	2.75 (1.37–5.53) *P* for trend = .002 1.33 (0.77–2.31) *P* for trend = .97 0.48 (0.25–0.92) *P* for trend = .05	IGF-I and IGFBP-3 mutually adjusted and adjusted for age, sex, ethnicity, cigarette smoking status, BMI, and family history of cancer; IGF-II not adjusted
Childhood leukemia	Petridou et al. *(293)*	Case–control; 122 case subjects and 122 hospital control subjects matched on age, sex, and maternal place of residence	50-ng/mL increase in serum IGF-I 1-μg/mL increase in serum IGFBP-3	0.95 (0.80–1.13) 0.72 (0.55–0.93)	IGF-I and IGFBP-3 mutually adjusted and adjusted for age, sex, and age of the sera

*Abbreviations used: BMI = body mass index ([weight in kg]/[height in m]^2); CI = confidence interval; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor-binding protein; PSA = prostate-specific antigen; RR = relative risk; WHR = waist-to-hip girth ratio.

†Cut points not presented.

‡Adjusted for IGFBP-3.

§Further analysis of a subset of specimens collected for the study by Wolk et al. *(295).*

‖RR similar after additional adjustment for IGF-I an IGFBP-3 concentrations.

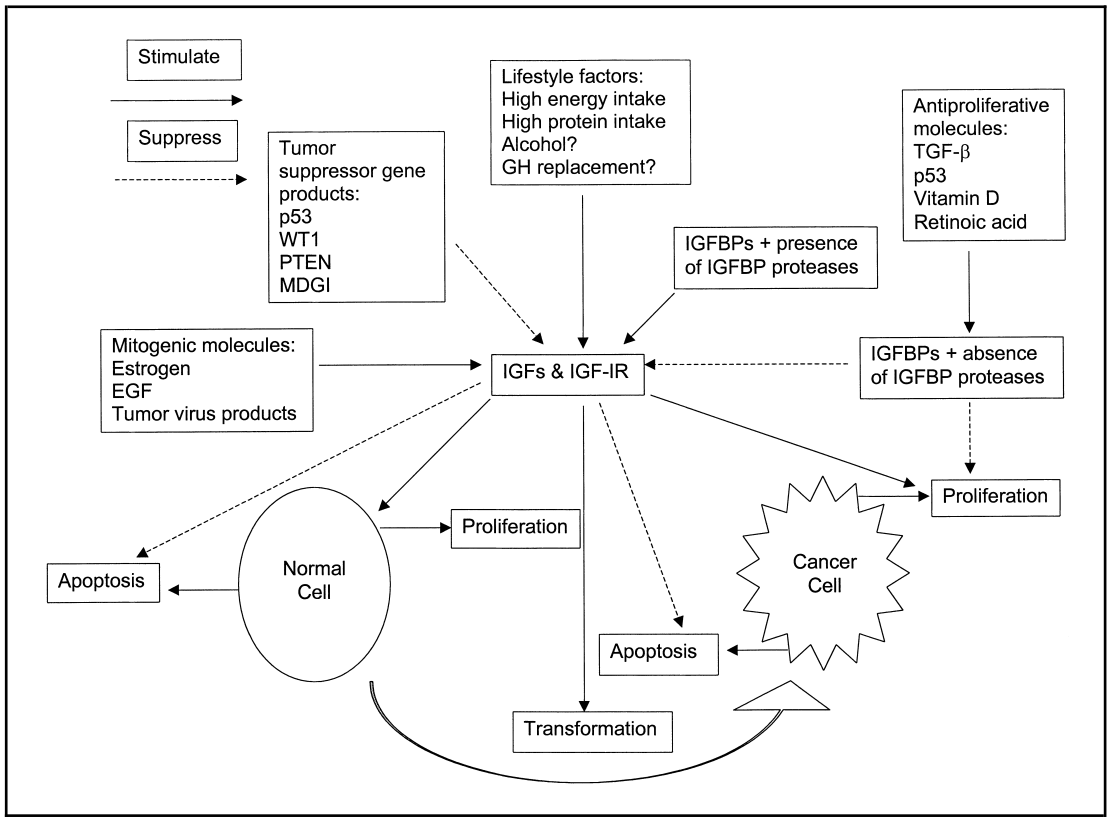

Fig. 1. Effects of insulin-like growth factors and insulin-like growth factor-I receptor on normal and cancerous cells and their relationships with mitogenic and antiproliferative molecules, tumor suppressor gene products, and lifestyle factors. **Solid arrows** indicate stimulation. **Dashed arrows** indicate suppression. **Question marks** indicate that the effect remains to be determined. **Abbreviations used:** EGF = epidermal growth factor; GH = growth hormone; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor-binding protein; IGF-IR = IGR-I receptor, TGF-β = transforming growth factor-β.

rently available clinical evidence, it would appear that IGF levels have little value in predicting cancer prognosis. This conclusion is supported further by the results of studies of blood levels of IGF-I, one *(269)* that involved comparing subjects with colonic adenomas with those with carcinoma of the colon and two *(3,295)* that examined the association between IGF-I levels and stage of prostate cancer. None of these three studies showed any evidence for differences between the compared groups.

Conclusion

The effects of IGFs on cells, their interplay with other molecules, and their relationships with lifestyle factors are summarized in Fig. 1. As a group of essential cell growth modulators, IGFs play a critical role in regulating cell growth and death. This important function of IGFs has led to speculation concerning their possible involvement in cancer development and growth.

Laboratory experiments demonstrate that IGFs are able to stimulate the growth of a wide variety of cancer cells and to suppress apoptosis. In addition to their direct effects on cancer cells, IGFs also interact synergistically with other mitogenic molecules and counteract antiproliferative molecules that are involved in cancer development and progression. Findings of experimental studies are supported by the observations of epidemiologic studies, which have shown that elevated levels of IGF-I in the circulation are associated with increased risk for several common cancers. In addition, an inverse association between IGFBP-3 and cancer risk has been observed in epidemiologic studies. However, since IGFBPs can either suppress or enhance the action of IGFs, the inverse relationship between IGFBP-3 and cancer risk has not been observed consistently in all studies. Further elaboration of the pathways and interrelationships that link members of the IGF family will increase our understanding of cancer etiology and pathogenesis and might yield opportunities for cancer prevention and therapy.

Evidence suggests that lifestyles characterized by a high-energy diet may affect the IGF system, which may, in turn, connect such lifestyles to high rates of cell proliferation and predispose cells to risk of malignant transformation. Currently unknown are the feasibility and validity of implementing dietary interventions to reduce IGF levels with the goal of preventing cancer. Studies that address this issue and the dose–response relationship between food intake and levels of IGFs in circulation may be of value in developing programs for cancer prevention and control.

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NOTES

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