INSULIN-LIKE GROWTH FACTORS AND NEOPLASIA

Michael N. Pollak, Eva S. Schernhammer‡ and Susan E. Hankinson‡*

The insulin-like growth factor 1 (IGF1) signalling pathway has important roles in regulating cellular proliferation and apoptosis. Converging results from epidemiological research and *in vivo* carcinogenesis models indicate that high levels of circulating IGF1 are associated with increased risk of several common cancers. Ongoing research seeks to clarify the mechanisms underlying these observations and to determine the extent to which IGF physiology influences patterns of cancer incidence. Various therapeutic strategies that target the IGF1 receptor have demonstrated impressive antineoplastic activity in laboratory models, and clinical trials of several novel drug candidates are planned.

AUTOCRINE
A form of bioregulation in which a secreted factor affects only the cell from which it was secreted.

GROWTH HORMONE
A polypeptide that is produced by the anterior pituitary gland that, among other functions, stimulates the liver to produce IGF1.

**Department of Oncology, McGill University and Lady Davis Research Institute, 3999 Rue Côte Sainte Catherine, Montréal, Québec H3T 1E2, Canada.*
‡Channing Laboratory and Department of Epidemiology, Harvard University, Boston, Massachusetts, USA.
Correspondence to M.N.P.
e-mail: michael.pollak@mcgill.ca

The insulin-like growth factor 1 (IGF1) signalling pathway arose early in evolution, possibly as a regulator of cellular proliferation in relation to nutrient availability[1]. This function is conserved in mammals — insulin and IGF1 have key roles in regulating cellular proliferation and apoptosis in relation to diet — but additional regulatory roles related to energy metabolism, body size, longevity and various organ-specific functions[2–5] have been acquired.

The role of IGF signalling in controlling rates of cell renewal has led to interest in the relevance of this regulatory system to both ageing and neoplasia[2,6,7]. IGF1 signalling stimulates proliferation and prolongs survival of cells propagated in tissue culture[4]. By contrast, ageing at the whole organism level proceeds more quickly with higher levels of IGF-related signalling[1,8,9]. Several model systems have provided evidence that proliferation and metastasis of cancer cells is increased by IGF1-receptor activation, either in relation to higher levels of circulating IGF1 in the host or to AUTOCRINE production of ligands by neoplastic cells[10]. Ongoing research is addressing potential clinical implications of these results.

This overview highlights key examples of recent biological and epidemiological research, and refers to more specialized reviews detailing laboratory and population studies.

Normal IGF physiology

The IGF system involves complex regulatory networks that operate at the whole organism, cellular and subcellular levels, as illustrated in FIGS 1,2 (for reviews, see REFS. 2,4,5,11). Key molecules involved are the ligands IGF1 and IGF2, the type 1 and type 2 IGF receptors (IGF1R and IGF2R, respectively), the IGF-binding proteins (IGFBPs), and the proteins involved in intracellular signalling distal to IGF1R, which include members of the insulin-receptor substrate (IRS) family, AKT, target of rapamycin (TOR) and S6 kinase.

IGF1 has characteristics of both a circulating hormone and a tissue growth factor. Most IGF1 found in the circulation is produced by the liver. Regulation of hepatic IGF1 production is complex. GROWTH HORMONE (GH) has a dominant role in upregulating *IGF1* gene expression, but its stimulatory influence is markedly reduced by malnutrition[12]. GH, in turn, is produced by the pituitary gland under the regulation of the hypothalamic factors somatostatin and growth-hormone-releasing hormone (GHRH). Initially, it was supposed that virtually all IGF1 originated in the liver and was transported by ENDOCRINE mechanisms to sites of action, but it is now recognized that IGF1 is also synthesized in other organs where autocrine or PARACRINE mechanisms of action are important. IGF2 is also expressed both in the liver and in extrahepatic sites, but is not tightly regulated by GH.

Summary

- Insulin-like growth factor 1 (IGF1) has characteristics of both a circulating hormone and a tissue growth factor.
- Circulating IGF1 levels vary considerably between normal individuals and there is evidence from epidemiological studies that individuals with levels at the higher end of the normal range have increased cancer risk. As this risk could apply to ~ 25% of the population, the attributable disease burden might be substantial, even though the relative risk associated with higher IGF1 levels is modest.
- Laboratory carcinogenesis models have provided data consistent with the population studies.
- Higher IGF1 levels might be associated with higher risk of a cancer diagnosis because of subtle influences on renewal dynamics of epithelial-cell populations: somatic cells of individuals with higher levels of IGF1 might show slightly higher proliferation rates and have a slightly increased chance of survival in the presence of genetic damage, because of the anti-apoptotic effects of IGF1. This would facilitate stepwise carcinogenesis. Higher IGF1 levels might also reduce the time interval between emergence of a transformed clone of cells and a clinically significant cancer.
- The syndrome of insulin resistance, characterized by increased insulin levels and obesity, is also associated with increased cancer risk and might involve similar mechanisms.
- In experimental models, the growth of many established cancers can be inhibited by pharmacological strategies that reduce IGF1-receptor (IGF1R) signalling; this observation will lead to clinical trials of new drug candidates, such as anti-IGF1R antibodies and IGF1R tyrosine kinase inhibitors.
- Dietary restriction confers protection against carcinogens and extends life expectancy in experimental models; there is evidence that both of these actions involve IGF signalling. Whereas higher levels of IGF signalling are associated with a shorter lifespan in model organisms, at the cellular level IGF1R activation activates anti-apoptotic pathways. A 'rate of living' model reconciles these observations.

Both IGF1 and IGF2 are ligands for IGF1R, which is a cell-surface tyrosine kinase signalling molecule. Following ligand binding, intracellular signalling pathways that favour proliferation as well as cell survival are activated. Initial phosphorylation targets for IGF1R include IRS proteins, and downstream signalling molecules include phosphatidylinositol 3-kinase, AKT, TOR, S6 kinase and mitogen-activated protein kinase (FIG. 2). IGF2R preferentially binds IGF2, but has no intracellular kinase domain, and might not act as a signalling molecule.

Bioavailability of IGFs is influenced by concentrations of specific IGFBPs[13]. At least six of these have been characterized, and their affinity for IGF1 and IGF2 is in the same order of magnitude as that of IGF1R. These proteins are present in the circulation as well as extravascular fluids. IGFBP3 provides most of the IGF-binding capacity of serum and greatly prolongs the circulating half-life of the IGFs. IGFBPs in extracellular-tissue fluid modulate interactions between IGF ligands and cell-surface IGF receptors. In different physiological contexts, the IGFBPs can either increase or decrease IGF signalling. This complexity is poorly understood; it probably arises because on the one hand IGFBPs prolong the half-lives of IGFs, but on the other they compete with receptors for free IGF1 and IGF2. Finally, there is increasing evidence that the IGFBPs have growth-regulatory actions that are independent of their capacity to bind IGFs. The physiological importance of these actions is an active area of research at present.

IGF pathophysiology in neoplasia

Ligands. The behaviour of many experimental IGF1R-positive cancers (for example, see REF. 14) is influenced by variations in the circulating levels of IGF1, indicating that these neoplasms are growth stimulated by IGF1 that is produced in tissues remote from the cancer. By contrast, some cancers might be stimulated by IGF1 or IGF2 that is synthesized locally in an autocrine or paracrine manner. Although these neoplasms would still be expected to be inhibited by strategies that block IGF1R, their behaviour would be predicted to be unrelated to circulating ligand levels. It is plausible that during the process of neoplastic progression, cancers might pass through a stage in which they are dependent on the host for the ligand, but later acquire the capacity for producing ligands in an autocrine manner, an event that might be associated with more aggressive behaviour. As methods for assessing levels of IGF1R activation advances, it will become possible to determine to what extent circulating levels of IGF1 are correlated with IGF1R signalling in normal tissues and in neoplasms at various stages of differentiation.

Regulation of *IGF2* expression is complex. It involves a non-translated mRNA known as H19 and silencing of one allele by a GENOMIC IMPRINTING mechanism[15]. Loss of imprinting or other regulatory failures that lead to increased *IGF2* expression would be predicted to confer a growth advantage. Observations that *IGF2* is the gene most overexpressed in colon cancers compared with normal colonic mucosa[16] and that loss of imprinting of *IGF2* represents a risk factor for colorectal cancer[17] indicate an important role for *IGF2* expression in cancer progression.

Receptors and downstream signalling. There is evidence from experimental systems[18] and studies of clinical specimens[19] that neoplastic progression, particularly in prostate cancer, might be associated with increased expression of IGF1R. However, amplification and overexpression seems to be less common for *IGF1R* than for *ERBB2* (also known as *HER2/NEU*) — a member of the epidermal growth factor receptor (EGFR) family that is

ENDOCRINE
A form of signalling whereby hormones are secreted into the circulation by specialized cells that affect the metabolism or behaviour of target cells that are distant from the site of hormone secretion.

PARACRINE
A form of bioregulation in which a secretion produced by one cell type in a tissue diffuses through the tissue and affects another cell type in the same tissue.

GENOMIC IMPRINTING
The epigenetic marking of a gene on the basis of parental origin, which results in monoallelic expression.

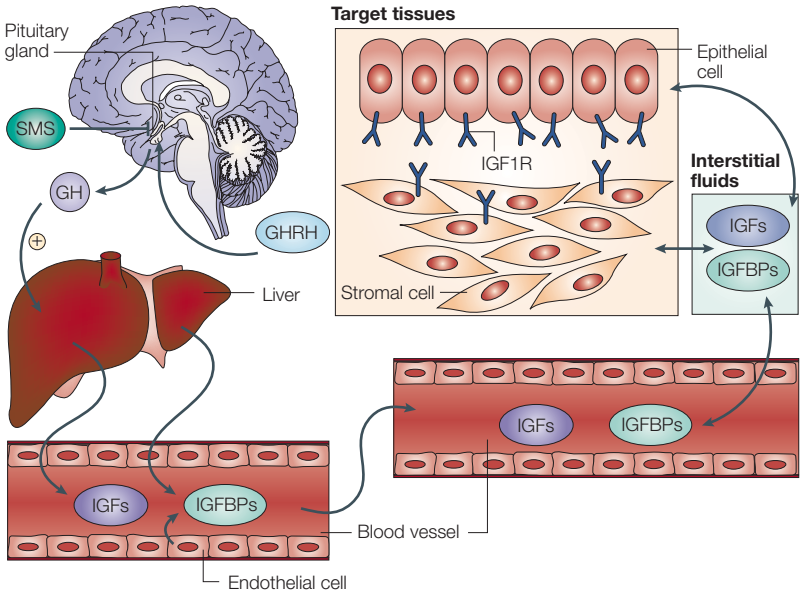

Figure 1 | **Regulation of circulating and tissue levels of insulin-like growth factors.** Most circulating insulin-like growth factors are produced in the liver. Hepatic IGF1 production is subject to complex regulation by hormonal and nutritional factors. Growth hormone (GH), which is produced in the pituitary gland under control of the hypothalamic factors growth-hormone-releasing hormone (GHRH) and somatostatin (SMS), is a key stimulator of IGF1 production. Various IGF-binding proteins (IGFBPs) are also produced in the liver. In IGF-responsive tissues, the ligands IGF1 and IGF2 as well as IGFBPs can be delivered through the circulation from the liver (an 'endocrine' source), but IGFs and IGFBPs can also be locally produced through autocrine or paracrine mechanisms. These mechanisms often involve interactions between stromal- and epithelial-cell subpopulations.

often found to be overexpressed in breast cancer. In many cases, IGF1R seems to have a role in regulating proliferation and differentiation even if its level of expression is low[20]. Downregulation of receptor expression might be associated with chronic stimulation by an autocrine IGF1 or IGF2 loop.

Signals from IGF1R can also become exaggerated or inappropriate because of molecular pathology that involves downstream elements. One common example is loss of function of the tumour-suppressor gene *PTEN*, which encodes a phosphatase that normally attenuates signals originating at tyrosine kinase receptors, including IGF1R (FIG. 2).

IGF2R is also implicated in neoplasia. Most studies indicate that this receptor does not transduce a signal and merely acts as a 'sink' for IGF2, which exerts its biological effects through IGF1R. This model provides a framework to explain the observation that IGF2R has properties of a tumour-suppressor gene: loss of IGF2R is correlated with increased IGF2-initiated IGF1R activation and increased proliferation[21].

IGFBPs. IGFBPs modulate bioavailability of IGFs in both the circulation and the cellular microenvironment[13]. The simplest model postulates that the dominant action of IGFBPs is to compete with receptors for ligands. So, under circumstances in which IGFBP levels are low, IGF mitogenic activity would be expected to be high. Many proteases that are present in tumour microenvironments, including metalloproteinases, caspases and prostate-specific antigen (PSA)[22] can digest IGFBPs and release free ligand. Production of proteases by a cancer might therefore increase IGF1R signalling. On the other hand, this model predicts that growth inhibitors might increase IGFBP expression, and this has been documented for anti-oestrogens, anti-androgens, transforming growth factor-β, deltanoids, retinoids and others[23,24].

Recent data indicate additional complexities. First, there is evidence that certain IGFBPs have IGF-independent growth-inhibitory or pro-apoptotic influences, and that neoplastic cells can develop resistance to these actions[13]. Second, in certain physiological contexts, IGFBPs seem to increase rather than reduce the mitogenic activity of IGFs[13]. These actions might involve lengthening the half-life of IGF1 and IGF2, or poorly characterized actions whereby IGFBPs deliver IGFs to IGF1R. Regardless of mechanism, there is evidence that in some situations, IGFBP expression can increase neoplastic behaviour and that measures that reduce IGFBP expression can inhibit tumour growth. Examples include experiments showing that inhibition of the increased expression of IGFBPs that follows castration delays the emergence of androgen-independent prostate cancer[25], and evidence that IGFBP2 expression is correlated with aggressive behaviour of gliomas and other cancers[26,27]. A recent observation requiring further study is that loss of function of *PTEN* is associated with upregulation of expression of IGFBP2 (C. Sawyers, personal communication).

IGF levels and cancer risk

Inter-individual variations in IGF levels. Before reviewing evidence for a relation between circulating levels of IGFs and cancer risk, it is important to understand that there is considerable variation of circulating levels of IGF1, IGF2 and IGFBP concentrations between normal individuals. Although clinical endocrinologists have long measured these concentrations to aid in the diagnosis of GH deficiency and ACROMEGALY, the traditional view has been that there is no biological or medical significance to the substantial variation that falls within the broad normal range between these pathological extremes. However, there is now evidence that this variation has implications regarding disease risk. Studies reviewed below indicate that the risk of common cancers is increased in individuals who have higher circulating levels of IGF1, compared with those who have levels at the lower end of the normal range. By contrast, among individuals with IGF1 concentrations within the normal range, risk of cardiac disease seems to vary inversely with circulating IGF1 levels[28,29].

Genetic factors. Genetic factors influence circulating IGF1 concentration[30]. Dozens of proteins are involved in the physiological systems that regulate IGF1 levels, and POLYMORPHIC VARIATION of the genes encoding any of these could influence circulating concentrations. Examples include genes encoding IGF1 itself; IGFBPs and their proteases; GH and its receptor; and somatostatin,

ACROMEGALY
A condition that results from the excess production of growth hormone in the anterior lobe of the pituitary gland.

POLYMORPHIC VARIATION
Occurrence, at a single genetic locus, of two or more alleles that differ in nucleotide sequence.

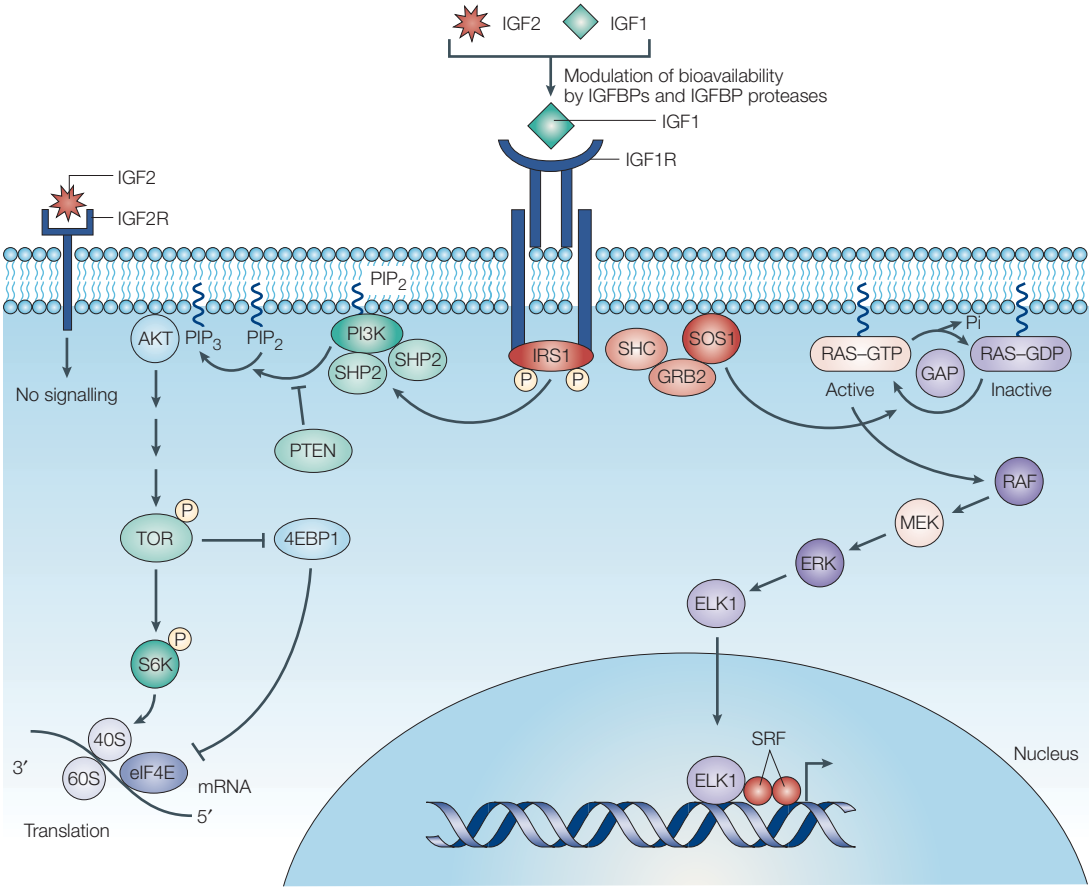

Figure 2 | Overview of insulin-like growth factor 1 receptor activation and downstream signalling. The insulin-like growth factor 1 receptor (IGF1R) is a tyrosine kinase cell-surface receptor that binds either IGF1 or IGF2. The local bioavailability of ligands is subject to complex physiological regulation and is probably abnormally high in many cancers. Ligands can be delivered from remote sites of production through the circulation or be locally produced. IGF-binding proteins (IGFBPs) and IGFBP proteases have key roles in regulating ligand bioavailability. IGFBPs prolong the half-life of IGFs, which has the potential to increase IGF1R activation. On the other hand, these proteins have affinity for IGFs comparable to IGF1R and there is competition between IGFBPs and IGF1R for available ligands in tissue microenvironments. This provides a basis for the inhibitory roles of IGFBPs on IGF1 signalling observed in many situations. There is evidence that certain IGFBPs also have direct, IGF-independent growth-regulatory actions. The IGF2R binds IGF2, but has no tyrosine kinase domain and appears to act as a negative influence on proliferation by reducing the amount of IGF2 available for binding to IGF1R. Certain IGFBP proteases (often produced by neoplastic cells) that cleave IGFBPs can release free ligand and thereby increase IGF1R activation. Following ligand binding to IGF1R, its tyrosine kinase activity is activated, and this stimulates signalling through intracellular networks that regulate cell proliferation and cell survival. Key downstream networks include the PI3K–AKT–TOR system and the RAF–MAPK systems. Activation of these pathways stimulates proliferation and inhibits apoptosis. This figure simplifies complex interacting regulatory networks. For many cell types, the key effects of signalling downstream to AKT relate to regulation of cell survival and mRNA translation, while the principal effect of signalling downstream to RAS involves regulation of cellular proliferation. 4EBP1, eukaryotic translation initiation factor 4E binding protein 1; eIF4E, eukaryotic translation initiation factor 4E; ERK, extracellular signal-regulated kinase; GRB2, growth-factor-receptor-bound protein 2; IRS1, insulin-receptor substrate 1; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; PI3K, phosphatidylinositol 3-kinase; PIP, phosphatidylinositol; PTEN, phosphatase and tensin homologue; S6K, S6 kinase; SHC, SRC-homology-2-domain transforming protein; SHP2, phosphatidylinositol 3-kinase regulatory subunit; SRF, serum response factor; TOR, target of rapamycin.

GHRH and their receptors. Only a few of these have so far been studied in the context of their ability to influence IGF1 levels within the normal range[31–34], but some are mutated in growth disorders associated with abnormal IGF1 levels[35,36]. Some[31,37], but not all[38], reports indicate that polymorphic variation within these genes influences cancer risk or prognosis. Common HAPLOTYPES might account for much of the variation in circulating levels of IGFs and their binding proteins[39].

HAPLOTYPE
A fixed pattern of several linked genetic polymorphisms.

Lifestyle factors. Nutrition has an important influence on circulating IGF1 levels. Starvation reduces both IGF1 levels[12] and intracellular signalling distal to IGF1R, at the level of TOR[40]. These regulatory systems might have evolved to minimize the energy and protein consumption related to renewal of epithelial-cell populations at times of inadequate nutrition. The observation that the protection against carcinogenesis conferred by dietary restriction is reversible by infusing IGF1 (REF. 41) indicates

a mediating role for IGF1 in the protective effect of calorific restriction on carcinogenesis. Similarly, observations that mutations that reduce IGF signalling are sufficient to extend lifespan in model organisms[1,8] indicate a mediating role for IGF signalling on the effects of dietary restriction on ageing.

More recent studies indicate that high levels of energy or protein intake are associated with modest increases in IGF1 levels[42–44]. In several studies, IGF1 levels were seen to increase with increasing dairy-product intake[42,43,45]. The underlying mechanism and significance of this relationship deserves further study, particularly as prostate cancer risk has been shown to increase with both IGF1 level[23] and dairy intake[46]. Micronutrients such as retinoids also influence circulating IGFBP3 levels, and this is modified by an *IGFBP3* polymorphism[33]. It is likely that ongoing research will uncover additional genetic factors that modify the influence of nutrition on IGF physiology. This work might allow the identification of certain individuals for whom specific dietary patterns have particularly important implications with respect to disease risk.

Hormones, including endogenous and exogenous steroids, have important influences on the GH–IGF1 axis. Both TAMOXIFEN and the potent synthetic oestrogen diethylstilbestrol are effective breast cancer treatments. Both have several mechanisms of action, but it is of interest that both suppress IGF1 levels[47,48]. Oral oestrogen-replacement therapy reduces circulating levels of IGF1, probably as a consequence of its direct delivery to the liver and suppression of hepatic *IGF1* gene expression[49]. This lowers circulating IGF1 levels, but might not reflect reduced IGF1 signalling in tissues. Oestrogen delivery by the transdermal route does not lower circulating IGF1 levels. In several experimental systems, oestrogens and IGFs act jointly to increase proliferation[50,51]. Polymorphisms that influence the function of IGF1R itself[34,52] or downstream signalling proteins would also be expected to add complexity to the relation between circulating IGF1 levels and IGF1R activation.

Circumstantial evidence. The initial evidence for an association between circulating IGF1 concentration and cancer risk was circumstantial. Small but significant increases in cancer risk with increasing height have been documented in many studies[53–56]. Height *per se* is unlikely to be a risk factor, but the hormonal determinants of height might influence cancer risk. IGF1 levels are, at most, weakly related to adult height, but are related to height early in life[57]. So, height might be weakly related to risk in part because it is weakly related to IGF1 exposure over the first decades of life. Birth weight and size have been associated with risk of breast[58,59], colorectal[60], prostate[61] and childhood cancers[62], and are positively correlated with cord-blood IGF1 levels[63]. Conversely, PRE-ECLAMPSIA is associated with reduced IGF1 levels and reduced breast cancer risk[64,65].

Mammographic density is strongly related to breast cancer risk (for a review, see REF. 66), but the mechanisms involved are unclear. There is evidence[67,68] for a positive relation between circulating IGF1 levels (or the ratio of IGF1 to IGFBP3 levels) and mammographic density. This raises the possibility that the relation between mammographic density and breast cancer risk exists, at least in part, because variability in density functions as a surrogate for variability in IGF1 physiology.

Racial factors also influence IGF1 and IGFBP3 levels, but it is important to not over-interpret what might be a coincidence. Black men have a higher risk for prostate cancer than other groups and have been observed to have lower levels of IGFBP3 (REF. 69), a protein that attenuates IGF signalling in experimental systems. Black women have higher IGF1 levels than other racial groups and also have a slightly higher risk of premenopausal breast cancer[70,71].

Although there are controversies, many studies (for reviews, see REFS 72,73) provide evidence that there is an excess of neoplastic disease among acromegalics, who have IGF1 levels above the normal range. Although this increased risk represents circumstantial evidence for an association between IGF1 and neoplasia, it is surprisingly modest in magnitude, in that very high IGF1 levels are not known to be associated with extreme cancer risk. This situation might relate to the fact that IGFBP3 and IGF1 are both increased in acromegaly. Also, there is obviously little modern experience with long-term follow-up of untreated acromegaly to determine cancer incidence.

Population studies: methodology. To examine the possibility that levels of a circulating analyte predict risk of a future cancer diagnosis, a NESTED CASE–CONTROL STUDY design is useful. This involves blood sampling of a large number of apparently healthy individuals before subsequent long-term clinical observation. After years of follow-up, individuals who have developed a particular cancer can be identified and assays can be performed on their stored blood samples, together with samples from an appropriate control group from the same cohort. The distribution of levels between the cases and controls is used to reach conclusions concerning the association of the analyte with subsequent risk. This method is useful because it minimizes the possibility that conclusions will be biased by effects of the disease itself on the analyte. This is an important consideration for studies of IGF1 and cancer risk, as it is known that the malnourishment that is associated with cancer CACHEXIA lowers IGF1 levels. A non-prospective study design — in which IGF1 levels are compared in blood taken from cases sampled after diagnosis and from a cancer-free control group — therefore presents potential difficulties in interpretation, particularly if the 'cases' have advanced cancer.

Assay technology for measuring IGFs, IGFBPs and related analytes is evolving rapidly[23]. As epidemiological research can require assessment of small differences between groups, it demands more accurate and sensitive assays than traditionally used clinical assay applications in the diagnosis of GH deficiency and acromegaly. It is necessary to ensure that a particular assay method is appropriate for a given set of samples, as varying amounts of proteolysis might occur between the time of

TAMOXIFEN
An anti-oestrogen drug that can be given to women with oestrogen-receptive tumours to reduce oestrogen-receptor activation.

PRE-ECLAMPSIA
A toxaemia of late pregnancy that is characterized by hypertension, oedema and proteinuria.

NESTED CASE–CONTROL STUDY
A population study where individuals with (cases) or without (controls) a disease are identified from within a larger cohort of individuals being followed for research purposes.

CACHEXIA
A state of ill health, weight loss and negative nitrogen balance that is often associated with advanced cancer.

blood sampling and assay, and antibodies vary in their specificity for different molecular species. This issue is particularly important for IGFBP3, which is present in the circulation as a mixture of polypeptides of varying length (because of proteolytic cleavage) and varying glycosylation and phosphorylation modifications, all of which might have physiological significance. Some of the discrepancies in the literature regarding the relation of IGFBP3 levels to subsequent cancer risk might relate to technical issues concerning assay methodology.

Population studies: results. Earlier reviews[10,23,24,74,75] have summarized both prospective and non-prospective data. Renehan *et al.*[76] recently published a comprehensive overview of population studies. The authors acknowledge controversies, but conclude, on the basis of a meta-analysis, that circulating IGF1 levels are related to risk of several common cancers. Because of space constraints, we restrict our review to larger prospective data sets (which are considered the most reliable) and to cancer types that have been studied independently by several groups (TABLE 1). Examples of recent interesting results that did not meet criteria for inclusion in TABLE 1 include evidence for associations between IGF1 levels and cancers of the uterine cervix, bladder and ovary[77–79].

Overall, a trend towards increasing risk with increasing levels of IGF1 is emerging. In the occasional study results are marked — for example, within the Physicians' Health Study Cohort, the association between IGF-related analytes and prostate cancer risk was stronger than the association between cholesterol and cardiovascular disease[80–82] — but overall the associations are modest. Of course, the impact of a risk factor that is common in a population and associated with modestly increased risk might exceed the disease burden attributable to strong risk factors that are encountered rarely.

It is important to point out that some studies did not detect an association of IGF1 levels with risk, particularly in the case of lung cancer[83]. This might be because IGF-related risk becomes relatively insignificant when carcinogenesis is driven by high levels of carcinogen exposure — the lung cancer cohorts differed from the cohorts of other cancer types, as they comprised heavy smokers. Interestingly, no association was seen between prostate cancer and IGF-related analytes among heavy smokers[84]. This remains unexplained, but a mechanism involving an effect of heavy smoking on IGF1 levels can not be ruled out. In the case of breast cancer, IGF1 has been related to risk in premenopausal women only, indicating the possible importance of levels in early life or an interaction with other hormones such as oestradiol.

The data for associations between IGFBP3 and cancer risk are not consistent, which might reflect that this analyte is simply unrelated to risk. Alternatively, ongoing research might uncover technical issues related to sample storage and measurement that explain the discrepancies. It is possible, for example, that risk varies with a particular molecular species of IGFBP3 that is present in the circulation.

TRAMP CARCINOGENESIS MODEL
A mouse model of prostate cancer that is characterized by spontaneous development of prostate tumours.

Laboratory models. Several *in vivo* carcinogenesis models have provided data that are compatible with an effect of host IGF1 physiology on cancer risk — these models are to be distinguished from those that study the influence of variations in IGF1 levels or IGF1 signalling on the behaviour of established cancers. It is interesting to note that most laboratory work concerning the relation of IGF1 to carcinogenesis was motivated by and followed the epidemiological research reviewed above. To the extent that these models showed trends in the same direction as those observed in the epidemiological research, the laboratory work in this area serves to increase the plausibility of the results from human populations.

Models in which circulating IGF levels are depleted by either liver-specific deletion of *IGF1* or expression of a GH antagonist provide evidence that lower IGF1 concentrations are associated with a significant reduction in breast cancer following exposure to chemical carcinogens[85,86]. Prostate cancer incidence in the well-characterized TRAMP CARCINOGENESIS MODEL[87] is substantially reduced in IGF1-deficient mice, whereas organ-specific overexpression of IGF1R increased prostate neoplasia[88]. Another example concerns hepatocarcinogenesis: overexpression of IGFBP1, which can attenuate IGF1R activation by sequestering ligands, inhibited carcinogenesis following exposure to the carcinogen diethylnitrosamine[89]. It is also of interest to note that certain cancer types are more frequent in large breeds of dogs, which have higher circulating IGF1 levels[90,91]. It is important to recognize that all of these models involve variations in IGF1 levels that are large compared with the more subtle variations in IGF1 physiology that exist between healthy humans. However, it is reasonable to expect that models of large differences that operate over relatively short times are able to simulate more subtle differences that might influence human carcinogenesis over decades.

Biological basis for a relation between IGF1 signalling level and cancer risk. The observed association between higher levels of IGF1 and cancer risk might arise because higher IGF1 levels are associated with acceleration of early carcinogenesis, as illustrated in FIG. 3. Carcinogenesis requires stepwise accumulation of genetic damage. This would be facilitated not only by faster rates of proliferation[92], but also by an environment that favoured, even slightly, survival (rather than programmed cell death) of stem cells that have undergone early genetic 'hits' — thereby increasing the pool of damaged cells available for second and subsequent hits. Higher levels of IGF1 would be expected to activate survival pathways that would make apoptotic death of damaged cells slightly less probable. When applied simultaneously to large numbers of at-risk cells over many years, even a small influence in this direction would serve to accelerate carcinogenesis. A separate mechanism might involve an effect of IGF1 on early progression of established neoplasms. This model postulates that IGF1R signalling is important in determining the time between full transformation of a single cell and the development of clinically significant disease. This is a potentially important issue, given evidence

Table 1 | **Population studies of serum IGF1 and IGFBP3 levels and cancer risk**

Study	Study population	Cancer risk related to IGF1 level*	Cancer risk related to IGFBP3 level*	References
Colorectal cancer				
Physicians' Health Study	193 cases, 318 contols	2.51 (1.15–5.46)	0.28 (0.12–0.66)	148
Nurses' Health Study	79 cases, 158 controls	2.18 (0.94–5.08)	0.28 (0.10–0.83)	149
New York University Women's Health Study	102 cases, 200 controls	1.23 (0.47–3.22)	1.23 (0.51–2.95)	129
North Sweden Health and Disease Cohort	110 cases, 336 controls	2.47 (0.93–6.53)	1.75 (0.72–4.22)	150
Chinese men living in Shanghai	135 cases, 661 controls	1.18 (0.55–2.53)	1.78 (0.86–3.70)	151
Prostate cancer				
Physicians' Health Study	530 cases, 540 controls	Early-stage disease: 1.2 (0.7–2.2) Late-stage disease: 5.1 (2.0–13.2)	Early-stage disease: 1.0 (0.6–2.2) Late-stage disease: 0.2 (0.1–0.6)	82,152
Baltimore Longitudinal Study of Aging	72 cases, 127controls	3.11 (1.11–8.74)	0.76 (0.30–1.94)	153
Northern Sweden Health and Disease Cohort	149 cases, 298 controls	1.72 (0.93–3.19)	1.83 (0.98–3.24)	154
The Washington County Serum Bank	30 cases, 60 controls	0.6 (0.1–2.9)	1.1 (0.3–3.8)	155
ATBC Cancer Prevention Study	100 cases, 400 controls	1.00 (0.54–1.87)	0.71 (0.36–1.39)	84
Breast cancer				
Nurses' Health Study	397cases, 620 controls	Premenopausal: 2.88 (1.21–6.85) Postmenopausal: 0.89 (0.51–1.55)	Premenopausal: ND Postmenopausal: ND	156
New York University Women's Health Study	287 cases, 706 controls	Premenopausal: 2.30 (1.07–4.94) Postmenopausal: 0.95 (0.49–1.86)‡	Premenopausal: 2.17 (0.99–4.76)‡ Postmenopausal: 1.08 (0.54–2.16)‡	157
Swedish cohorts	513 cases, 987 controls	Premenopausal: 0.63 (0.29–1.39)‡ Postmenopausal: 1.29 (0.80–2.07)‡	Premenopausal: 1.37 (0.65–2.91)‡ Postmenopausal: 1.46 (0.92–2.32)‡	158
Kaiser Permanent Medical Care Program	126 cases, 126 controls	Premenopausal: 3.49 (0.65–18.7) Postmenopausal: 0.77 (0.23–2.56)	Premenopausal: 5.28 (1.13–24.7) Postmenopausal: 0.32 (0.07–1.41)	159
Italian cohort (ORDET)	133 cases, 503 controls	Premenopausal: 3.12 (1.13–8.60) Postmenopausal: 0.58 (0.24–1.36)	Premenopausal: 2.31 (0.97–5.53) Postmenopausal: 0.73 (0.30–1.74)	127
Two prospective cohorts — EPIC and PPHV	149 cases, 333 controls	Premenopausal: ND Postmenopausal: 1.1 (0.6–2.1)‡	Premenopausal: ND Postmenopausal: 1.6 (0.7–3.5)‡	160
Lung cancer				
CARET	159 cases, 297 controls	0.64 (0.31–1.33)	2.35 (1.13–4.92)	83
Japan Collaborative Cohort Study	194 cases, 9351controls	1.17 (0.78–1.77)	0.67 (0.45–1.01)	161
Shanghai, China	230 cases, 659 controls	0.73 (0.43–1.57)	0.56 (0.30–1.03)	162
New York University Women's Health Study	93 cases, 186 controls	0.79 (0.29–2.19)	0.90 (0.36–2.25)	163

*Highest versus lowest quantile relative risk (95% confidence interval). All relative risks are adjusted for the study matching factors and insulin-like growth factor 1 (IGF1) or IGF-binding protein 3 (IGFBP3), respectively, unless otherwise noted (‡). ATBC, α-tocopherol, β-carotene; CARET, β-Carotene and Retinol Efficacy Trial; EPIC, European Prospective Investigation into Cancer and Nutrition; ND, not determined; ORDET, Hormones and Diet in the Aetiology of Breast Cancer.

(best documented in prostate cancer[93]) that early carcinogenesis occurs very commonly by middle age and that risk of clinically detectable cancer depends on inter-individual differences in probability of progression[94]. These proposed mechanisms are not mutually exclusive.

IGF1 receptor: a target for cancer treatment

The concept of receptor targeting is now well established in anticancer therapeutics. Androgen and oestrogen receptors are molecular targets that have led to the development of widely used oestrogen- and androgen-receptor antagonists for treatment of prostate and breast cancer. More recently, success in the clinic of compounds that target tyrosine kinase receptors, such as imatinib (Glivec), and compounds that interfere with the function of receptors in the EGFR family, such as trastuzumab (Herceptin), have demonstrated that the paradigm of receptor targeting can be extended beyond steroid-hormone receptors.

Progress in defining the pathophysiological role of signalling at and downstream of IGF1R in neoplasia might lead to the development of novel targeting strategies and to the definition of criteria that identify cancers that might be responsive to these treatments. Not long after IGF1R was reported to be present in surgically resected tumour specimens, and initial speculation that IGF1R might represent a therapeutic target[95], it was shown that administration of a blocking antibody

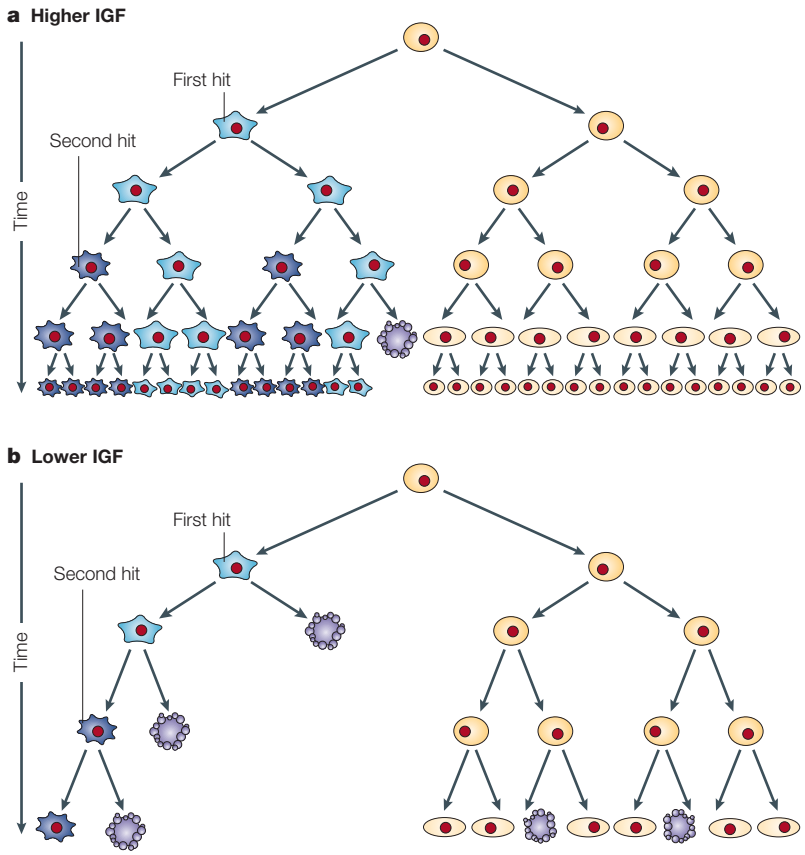

Figure 3 | **Model of the influence of insulin-like growth factor 1 signalling on the stepwise accumulation of somatic-cell genetic damage in carcinogenesis.** The model of stepwise accumulation of genetic damage leading to carcinogenesis can be extended to include influences of insulin-like growth factor 1 (IGF1) signalling. These include favouring cellular proliferation over arrest and cellular survival over apoptosis. This model provides a preliminary biological framework to account for the observed association of higher levels of IGF1, or IGF1 receptor (IGF1R) activation, with cancer risk in epidemiological and laboratory studies. The model predicts that stepwise accumulation of genetic damage is facilitated in individuals with higher IGF1 levels because in these individuals there is a slightly higher rate of cell division (increasing the risk of errors) and, perhaps more importantly, because the probability of appropriate apoptosis of cells with a small number of 'hits' would be slightly reduced in a microenvironment with higher levels of IGF1R activation. The figure greatly exaggerates the magnitude of the hypothesized differences between 'high IGF' and 'low IGF' individuals in proliferation and apoptosis for purposes of illustration. Very small differences in these parameters, if applied to the very large renewing cell populations of organs such as the colon over a timespan of decades could influence the probability of emergence of a fully transformed clone. Colours indicate the following: yellow, normal cells; pale blue, cells containing one mutation or hit; dark blue, cells containing two mutations or hits; purple, apoptotic cells.

directed against this receptor slowed the *in vivo* proliferation of human breast cancer xenografts[96]. This experimental result did not lead to immediate translational research, as it was obtained years before the now widespread therapeutic use of antibodies and also pre-dated current interest in tyrosine kinase receptors as molecular targets in oncology. Nearly 15 years later, interest in targeting IGF1R has become widespread[7,97,98].

Preclinical models. Work with transgenic mice (for example, REF. 14) adds to previous laboratory evidence[10,99,100] that IGF1 provided by the host stimulates aggressive behaviour of established cancers. Recent research has shown that targeting IGF1R leads to impressive antineoplastic activity in many *in vitro* and *in vivo* models of common human cancers. Strategies that have been used are illustrated in FIG. 4 and include administration of molecules to interfere with ligand binding to IGF1R, such as IGFBPs, peptide or small-molecule competitive binding antagonists, or blocking anti-receptor antibodies[101,102,164]; antisense or SMALL INTERFERING RNA strategies to reduce receptor expression[103]; introduction of a dominant-negative IGF1R to interfere with receptor action[104–106]; use of small-molecule IGF1R-specific tyrosine kinase inhibitors[107–109]; and targeting signalling pathways downstream of IGF1R with agents such as AKT or TOR inhibitors[40,110–112,165].

Reduction of IGF1 levels by the use of somatostatin analogues[113], GHRH antagonists[114] or GH antagonists[115] has also been proposed, as these approaches show efficacy in preclinical models. Clinical trials of somatostatin analogues in advanced breast cancer have been disappointing, but the long-term reduction in IGF1 levels achieved by this strategy was only modest[116], probably because of the development of compensatory mechanisms, such as increased GHRH secretion, that serve to attenuate the suppressive effect of somatostatin analogues on GH and IGF1 levels.

Evidence that functional IGF1 receptors are necessary for transformation induced by various means, including oncogene activation or chemical carcinogens[117], has led to optimism that IGF1R blockade might be of therapeutic value in a broad spectrum of malignancies[97,118]. Apart from possible activity as a single agent, IGF1R blockade might potentiate various existing therapies, including cytotoxic agents, radiotherapy and therapies that target various steroid or peptide-hormone receptors. The hypothesis that targeting the IGF1R will increase the efficacy of other antineoplastic treatments is based on evidence that survival signals originating at this receptor limit the efficacy of other treatments designed to induce apoptosis. For many cell lines, *in vitro* dose-response curves of apoptosis-inducing cytotoxic agents can easily be shifted by varying the concentration of IGF1 in the experimental system. In addition, it is possible that the development of resistance to certain therapies involves increased IGF1R activation. There is, for example, *in vitro* evidence that increased IGF1R signalling confers resistance to compounds that target ERBB2 and that IGF1R blockade can restore sensitivity to these compounds[119]. This evidence, together with other examples such as synergistic induction of apoptosis when small-cell lung cancer is targeted by both c-KIT and IGF1R inhibitors[120], indicates that IGF1R blockade might sensitize certain cancers to other kinase inhibitors.

Insulin and IGF1 half-receptors can form heterodimers[121], but the tissue distribution of these molecules remains a research topic. It is not yet clear to what extent, if any, specific IGF1R-targeting strategies will interfere with function of hybrid receptors.

SMALL INTERFERING RNAS
Small RNAs, typically 21–23 nucleotides in length, that can interfere with expression of specific genes.

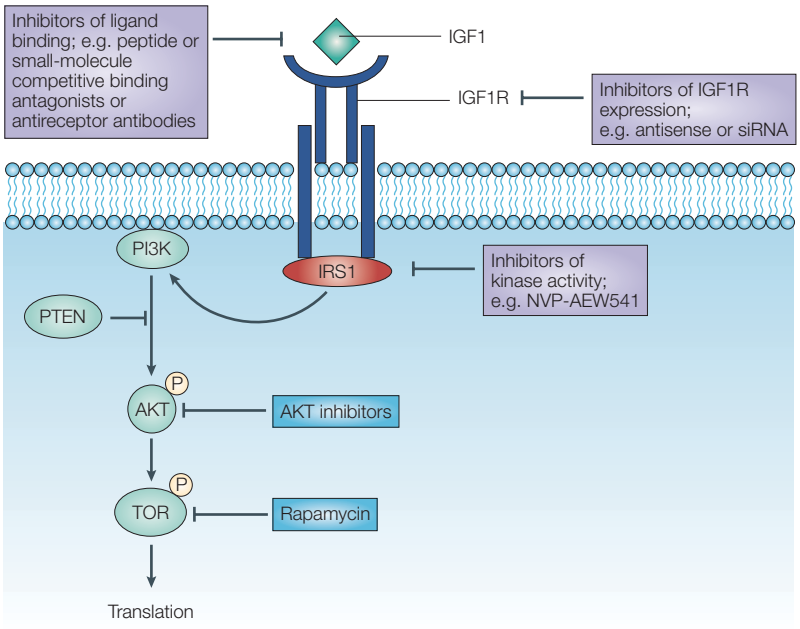

Figure 4 | **Insulin-like growth factor 1 receptor targeting: therapeutic strategies.** Work is underway by many groups to develop pharmacological strategies to reduce signalling at and downstream of the insulin-like growth factor 1 receptor (IGF1R), in the hope that this will lead to compounds that are useful in cancer treatment. Approaches that will soon be tested clinically following demonstration of antineoplastic activity in laboratory studies include the use of blocking antibodies directed against the extracellular portion of the receptor and small-molecule tyrosine kinase inhibitors with specificity for IGF1R. Small interfering RNA (siRNA) and antisense strategies to reduce receptor expression, as well as transfection of altered or truncated IGF1R proteins that act in a dominant-negative fashion to interfere with receptor function are additional approaches that have been effective in laboratory studies. There is also great interest in therapeutic strategies that target signalling pathways downstream of IGF1R. Important examples include AKT inhibitors, and TOR inhibitors such as rapamycin and its analogues. IRS1, insulin-receptor substrate 1; PI3K, phosphatidylinositol 3-kinase; TOR, target of rapamycin.

Towards clinical trials. Preclinical studies of IGF1R targeting strategies have provided evidence of efficacy comparable to that obtained for other antineoplastic strategies that have subsequently been found to be clinically useful. Some methods that successfully targeted IGF1R experimentally, such as transfecting cells with a dominant-negative receptor, are not immediately ready for clinical evaluation because of general issues related to optimization of gene-therapy methods. Others, such as the use of orally active small-molecule IGF1R kinase inhibitors or antireceptor antibodies, are expected to be evaluated in clinical trials.

The design of such trials will be challenging: there is a need to consider single agent activity, but as noted above, preclinical research indicates that some of the most promising applications might involve combinations with current cytotoxic or endocrine therapies. With respect to anticipated toxicity, the possibility that therapies directed against IGF1R will lack sufficient specificity to avoid co-targeting the insulin receptor must be considered, and careful assessment of glucose metabolism will be required. While dose-limiting toxicity involving increased blood glucose has not been seen in preclinical studies of IGF1R-targeting therapies so far, vigilance is required. A recent study[166] documented severe insulin resistance and diabetes due to an inactivating mutation in AKT, indicating that complete suppression of certain signalling pathways distal to the insulin and/or IGF1R might well have adverse effects.

It is not obvious what cancer types are most likely to respond to IGF1R targeting. Preclinical evidence provides a rationale for clinical trials in multiple myeloma, breast, prostate and colon cancer, sarcomas, and some other cancers. If the anatomical site of the cancer can not be relied on to predict therapeutic response, it will be particularly important to discover molecular 'signatures' associated with high probability of clinical benefit of IGF1R targeting. Early research in this area indicates that IGF1R overexpression in biopsy specimens might not be a useful predictor of responsivity to IGF1R-targeting drugs. This is in contrast to experience in prediction of efficacy of agents that block signalling through ERBB2, for which receptor levels have been found to be useful in predicting efficacy. This might be because the pathophysiology of ERBB2 activation almost always involves receptor overexpression, whereas IGF1R activation seems to involve several mechanisms that lead to increased signal transduction. Recent work[122] indicates that specific somatic-cell mutations in EGFR might allow prediction of sensitivity to small-molecule EGFR inhibitors; the possibility that an analogous situation exists for IGF1R is under investigation. Phosphorylated IGF1R levels and levels of IGF2 expression (indicating the presence of an active IGF2–IGF1R autocrine loop) in cancer tissue are further examples of candidate predictors of response to IGF1R-targeting therapies that are being evaluated.

It would not be surprising if effective IGF1R blockade was associated with a compensatory increase in circulating IGF1 levels, as receptors involved in IGF1 homeostatic control would probably be blocked in parallel with the target receptors on neoplastic cells. However, early experimental results indicate that the increase in IGF1 level is insufficient to overcome the pharmacological blockade. Furthermore, this phenomenon might be useful: experimental results raise the possibility that changes in IGF1 levels, as well as IGF1R phosphorylation levels in skin biopsies — analogous to similar studies used in evaluating EGFR blockade[123] — might be useful as end points in early dose-finding studies.

In certain experimental systems (for example, see REF. 104) IGF1R targeting shows antimetastatic activity. This might relate to evidence that IGF1 stimulates ANGIOGENESIS, in part by upregulating VEGF expression[124]. Although this implies potential application of IGF1R-targeting strategies in ADJUVANT TREATMENT settings, it is clear that trials in individuals with advanced disease represent necessary first steps to establish dose and toxicity.

Further research directions

As many aspects of IGF physiology are incompletely understood, clarification of IGF pathophysiology in neoplasia is challenging. Indeed, potential relevance to oncology has been one of the factors accelerating basic research concerning IGFs. In this section we provide examples of active research areas.

ANGIOGENESIS
Development of new blood vessels to supply blood to a cancer, a process stimulated by vascular endothelial growth factor and that is necessary for micrometastases to grow to a clinically detectable size.

ADJUVANT TREATMENT
Following resection of a primary cancer, adjuvant treatment of an apparently well patient who might have micrometastases is given to prevent the later development of microscopic metastatic disease.

How are variations in circulating IGF1 levels related to variations in IGF1R signalling? It is often assumed that IGF1 serum levels can be used as a surrogate for IGF1 levels in interstitial fluid or for IGF1R signalling. Direct evidence to test this plausible hypothesis is lacking at present, but might become available as the methodology for measuring IGF1R activation in tissues improves. Experimental evidence that cellular proliferation increases with increasing circulating IGF1 concentration[74,125] is consistent with this hypothesis. It is likely that the relation between the circulating levels and tissue bioactivity is complex. For example, higher circulating levels of IGFBPs might increase IGF1 concentration by increasing its circulating half-life, but this might not reflect an increase in receptor activation at the tissue level. Polymorphisms that influence the function of IGF1R itself[34,52] or downstream signalling proteins would also be expected to add complexity to the relation between circulating IGF1 levels and IGF1R signalling.

What is the best IGF1R-targeting strategy to test clinically? Recent successes in development of small-molecule IGF1 tyrosine kinase inhibitors, blocking antibodies against the IGF1 receptor, and agents that block signalling downstream to the receptor pose challenges to translational scientists seeking to design clinical trials. Kinase inhibitors have potential advantages including convenient oral administration. On the other hand, strict specificity for IGF1R has been documented only at certain concentrations under carefully controlled *in vitro* conditions. Therefore, it is difficult to predict *a priori* to what extent these agents will be specific for IGF1R during long term *in vivo* use, where tissue concentrations might vary. The potential for loss of strict specificity for IGF1R might be problematic from the point of view of toxicities, but on the other hand might be advantageous if other kinase targets are contributing to the molecular pathology of the cancer being treated. If toxicity is problematic for the kinase inhibitors, then receptor-targeting antibodies might have important advantages.

Targeting downstream signalling elements such as AKT that integrate signals from several kinds of cell-surface receptors has the potential to circumvent certain resistance mechanisms that might limit efficacy of blockade of IGF1R or other cell-surface receptors. Blockade of any particular type of cell-surface receptor might create selection pressure favouring survival of tumour cells that can compensate for blockade by increased signalling through alternate receptors. Resistance to ERBB2 blockade by increasing IGF1R signalling[119] (or vice versa) *in vitro* indicates that this process is plausible, but studies in clinical specimens have not been undertaken so far. On the other hand, the potential toxicity of agents that interfere with signalling originating at several receptors might exceed that associated with agents that target a specific receptor.

The general goal of evaluating the efficacy of IGF1R targeting in clinical trials does not presently imply a specific targeting strategy, a particular pharmacodynamic evaluation to assure successful target blockade, a specific tumour type or any specific therapeutic combinations with various current therapies. Therefore, initial clinical trial design will probably involve empirical decisions.

What is the impact of insulin resistance on IGF1R signalling and cancer risk? Insulin resistance is a metabolic syndrome characterized in part by hyperglycaemia despite high levels of insulin and is commonly found in obese individuals. It involves decreased expression of IGFBP1 (REF. 13), which might increase IGF1R activation in certain tissues. Studies examining weight or serum markers of insulin resistance to cancer risk have detected relationships with risk of endometrial[126], breast[127], prostate[128] and colon cancer[129], together with an adverse effect on prognosis of breast[130] and prostate[131] cancer. It remains to be determined to what extent the mechanisms underlying these emerging relationships are similar to those underlying IGF1-related risk factors and to what extent they involve the insulin receptor. An important research area concerns the potential influence of insulin-sensitizing drugs such as thiazolidinediones on cancer risk and cancer behaviour.

These are significant questions in part because of the need to address public-health implications of the steep rise in obesity and insulin resistance that is occurring in many countries[132], particularly among children. These trends have worrying implications for cancer incidence. Furthermore, as height at puberty is related to IGF1 level, the secular trend towards increasing height that has been observed in certain populations over the past century[133] indicates the possibility that age-specific IGF1 levels might have been rising during this time period, perhaps in relation to dietary changes such as increased energy and protein intake. The postulated increases of IGF1 and insulin levels coincide with increasing incidence of cancers that are associated with a 'Western' diet and lifestyle[134–136], but further research is needed to determine if there is a causal relationship.

Is the relation between IGF1 and cancer risk relevant to GH therapy or to ageing? GH-supplementation therapy to achieve IGF1 levels that are higher than the age-specific population normal is controversial[137]. This use of GH has become surprisingly popular following publication of short-term studies indicating that it has short-term anabolic and 'anti-ageing' effects[138], even though these findings have been questioned[139]. It is sobering to recognize that whereas pharmacological measures to raise IGF1 levels have been proposed to retard ageing, results from model organisms indicate that such measures might have the opposite effect over the long term[1,8]. The evidence concerning a relation between cancer risk and IGF1 levels would indicate that pharmacological methods to increase IGF1 beyond age-specific norms should be approached with caution, and that when long-term GH therapy is medically indicated to treat deficiency states, efforts should be made to titrate the GH dose to achieve IGF1 levels close to the age-specific mean levels in an appropriate reference population[140,141].

In animal models ranging from *Caenorhabditis elegans* to mice, life expectancy has been found to be inversely related to IGF signalling[1,8]. Homozygosity for the *Lit* mutation, which inactivates the GHRH receptor, results in small mice with subnormal levels of circulating IGF1 (REF. 99). Interestingly, these animals provide an environment that is less permissive for neoplastic proliferation than controls[87,99] and also have a longer life expectancy than controls[142]. Consistent with these results, mice heterozygous for the IGF1 receptor were recently shown to have extended life expectancy[143]. These examples provide an interesting contrast to mice with increased p53 activity[144,145], which are resistant to carcinogenesis but show premature ageing.

What mechanisms might underlie the experimental results that indicate increased life expectancy and reduced cancer risk in animals with low IGF1, and yet be compatible with the anti-apoptotic and proliferation-stimulating effects of IGF1 at the cellular level? One concept that deserves re-examination is the notion of 'rate of living' (FIG. 5). It is plausible that somatic-cell DNA damage, which contributes to both carcinogenesis and ageing, accumulates as a function of the number of cell divisions following ovum fertilization. In individuals with higher IGF1 levels, the rate of cell division in renewing somatic tissues might be greater than in individuals with lower levels. In a Darwinian sense, this would be expected to be associated with certain advantages, such as more rapid wound healing and earlier achievement of adult body size. At the cellular level, a consequence of the hypothesized higher rate of cell division associated with higher IGF1 levels would be that at any arbitrary organism age, those individuals with higher IGF1 levels would have undergone a higher number of somatic-cell divisions in renewing epithelial-cell populations. By the 'clock' of number of cell divisions, individuals with higher IGF1 levels would be ageing faster. Those with lower IGF1 levels, by spacing cell divisions more widely, would be ageing more slowly with reference to an external clock. Consistent with the model is early evidence from murine, primate and human studies that epithelial-cell turnover rates vary with IGF1 levels[74,125,146]. Quantitative studies of this important issue are limited by precision of current methods: variability between persons in mean half-life of colon epithelial cells by as little as a few hours would result in a huge difference in the number of cell divisions over decades of life. Evidence that mice strains that grow to larger sizes have shorter life expectancies[147] is consistent with the model. The fact that cancer risk increases with age whereas IGF1 levels decline with age does not represent evidence against the hypothesis, because in stepwise carcinogenesis DNA damage accumulates over decades; important determinants of cancer risk late in life operate in early and midlife.

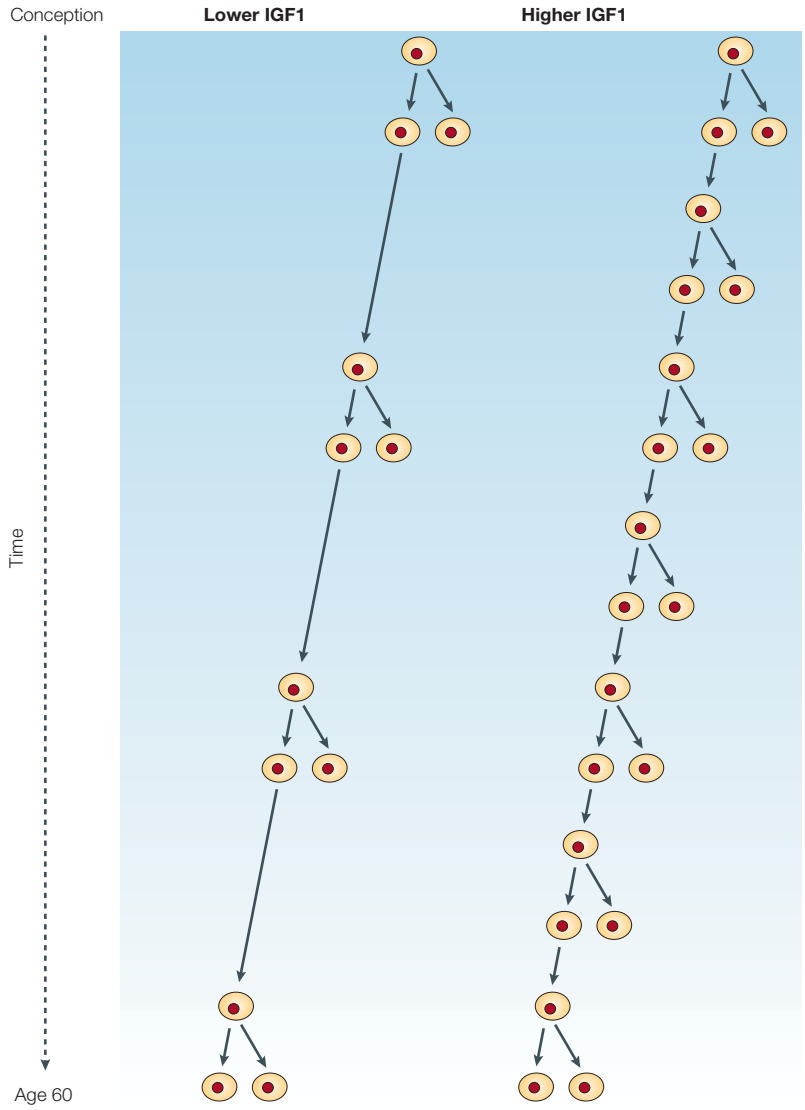

Figure 5 | **Why is life expectancy increased when insulin-like growth factor 1 levels are reduced?** Experimental results provide convincing evidence that in several experimental organisms, decreased insulin-like growth factor 1 (IGF1) signalling is associated with increased lifespan, even though in cell-culture systems reduced IGF1-receptor (IGF1R) activation increases the likelihood of cell death. A model to account for the increased lifespan associated with reduced IGF1 signalling is related to the classic 'rate of living' hypothesis. It is plausible that the process of ageing is related to the number of cell divisions since conception (although other factors are also involved). If the rate of cell turnover increases with higher levels of activation of IGF1R or related receptors, then at any fixed chronological age, there will have been more cell divisions in the ancestry of IGF-responsive cells of individuals with higher levels of receptor activation, compared with individuals with lower levels of activation. By the measure of 'number of cell divisions since conception', at an arbitrary number of years since conception, the individual on the right has aged faster than the individual on the left. If the process of ageing proceeds at least in part as a function of the number of cell divisions since conception, rather than as a function of elapsed time since conception, the individual on the left would live longer.

Conclusion

More than a decade has passed since the hypothesis that IGF1 signalling is relevant to human neoplasia was formulated. Although laboratory research implicates many molecular signals in the neoplastic process, the IGF system provides a rare example where evidence is accumulating from both population studies and laboratory research. In the coming years, it is likely that conclusions relevant to cancer prevention and treatment will emerge from large-scale population studies concerning risk, clinical trials of IGF1R-targeting therapies and ongoing laboratory work.

1. Longo, V. D. & Finch, C. E. Evolutionary medicine: from dwarf model systems to healthy centenarians? *Science* **299**, 1342–1346 (2003).
2. Baserga, R., Peruzzi, F. & Reiss, K. The IGF-1 receptor in cancer biology. *Int. J. Cancer* **107**, 873–877 (2003).
3. Giudice, L. C. Maternal-fetal conflict—lessons from a transgene. *J. Clin. Investig.* **110**, 307–309 (2002).
4. Jones, J. I. & Clemmons, D. R. Insulin-like growth factors and their binding proteins: biological actions. *Endocr. Rev.* **16**, 3–34 (1995).
5. Nakae, J., Kido, Y. & Accili, D. Distinct and overlapping functions of insulin and IGF-I receptors. *Endocr. Rev.* **22**, 818–835 (2001).
6. Holly, J. M. Insulin-like growth factor-I and new opportunities for cancer prevention. *Lancet* **351**, 1373–1375 (1998).
7. Burroughs, K. D., Dunn, S. E., Barrett, J. C. & Taylor, J. E. Insulin-like growth factor-I: a key regulator of human cancer risk? *J. Natl Cancer Inst.* **91**, 579–581 (1999).
8. Tatar, M., Bartke, A. & Antebi, A. The endocrine regulation of aging by insulin-like signals. *Science* **299**, 1346–1351 (2003).
9. Arantes-Oliveira, N., Berman, J. R. & Kenyon, C. Healthy animals with extreme longevity. *Science* **302**, 611 (2003).
10. Khandwala, H. M., McCutcheon, I. E., Flyvbjerg, A. & Friend, K. E. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. *Endocr. Rev.* **21**, 215–244 (2000).
11. De Meyts, P. & Whittaker, J. Structural biology of insulin and IGF-1 receptors: implications for drug design. *Nature Rev. Drug Discov.* **1**, 769–783 (2002).
12. Thissen, J. P., Ketelslegers, J. M. & Underwood, L. E. Nutritional regulation of the insulin-like growth factors. *Endo. Rev.* **15**, 80–101 (1994).
13. Firth, S. M. & Baxter, R. C. Cellular actions of the insulin-like growth factor binding proteins. *Endocr. Rev.* **23**, 824–854 (2002).
14. Wu, Y., Yakar, S., Zhao, L., Hennighausen, L. & LeRoith, D. Circulating insulin-like growth factor-1 levels regulate colon cancer growth and metastasis. *Cancer Res.* **62**, 1030–1035 (2002).
15. Arney, K. L. H19 and IGF2 — enhancing the confusion? *Trends Genet.* **19**, 17–23 (2003).
16. Zhang, L. *et al.* Gene expression profiles in normal and cancer cells. *Science* **276**, 1268–1272 (1997).
Provides evidence that IGF2 is the most overexpressed gene in colorectal cancer tissue relative to normal colorectal mucosa; an observation consistant with the notion that autocrine expression of this gene can contribute to neoplastic behaviour.
17. Cui, H. *et al.* Loss of IGF2 imprinting: a potential marker of colorectal cancer risk. *Science* **299**, 1753–1755 (2003).
18. Nickerson, T. *et al. In vivo* progression of LAPC-9 and LNCaP prostate cancer models to androgen independence is associated with increased expression of insulin-like growth factor I (IGF-I) and IGF-I receptor (IGF-IR). *Cancer Res.* **61**, 6276–6280 (2001).
19. Hellawell, G. O. *et al.* Expression of the type 1 insulin-like growth factor receptor is up-regulated in primary prostate cancer and commonly persists in metastatic disease. *Cancer Res.* **62**, 2942–2950 (2002).
20. Tennant, M. K. *et al.* Protein and messenger ribonucleic acid (mRNA) for the type 1 insulin-like growth factor (IGF) receptor is decreased and IGF-II mRNA is increased in human prostate carcinoma compared to benign prostate epithelium. *J. Clin. Endocrinol. Metab.* **81**, 3774–3782 (1996).
21. O'Gorman, D. B., Weiss, J., Hettiaratchi, A., Firth, S. M. & Scott, C. D. Insulin-like growth factor-II/mannose 6-phosphate receptor overexpression reduces growth of choriocarcinoma cells *in vitro* and *in vivo*. *Endocrinology* **143**, 4287–4294 (2002).
22. Cohen, P. *et al.* Prostate-specific antigen (PSA) is an insulin-like growth factor binding protein-3 protease found in seminal plasma. *J. Clin. Endo. Met.* **75**, 1046–1053 (1992).
23. Pollak, M. Insulin-like growth factors (IGFs) and prostate cancer. *Epidemiol. Rev.* **23**, 59–66 (2001).
24. Pollak, M. Insulin-like growth factor physiology and cancer risk. *Eur. J. Cancer* **36**, 1224–1228 (2000).
25. Miyake, H., Pollak, M. & Gleave, M. E. Castration-induced up-regulation of insulin-like growth factor binding protein-5 potentiates insulin-like growth factor-I activity and accelerates progression to androgen independence in prostate cancer models. *Cancer Res.* **60**, 3058–3064 (2000).
26. Elmlinger, M. W. *et al. In vivo* expression of insulin-like growth factor-binding protein in human gliomas increases with tumor grade. *Endocrinoogy* **142**, 1652–1658 (2001).
27. Baron-Hay, S., Boyle, F., Ferrier, A. & Scott, C. Elevated serum insulin-like growth factor binding protein-2 as a prognostic marker in patients with ovarian cancer. *Clin. Cancer Res.* **10**, 1796–1806 (2004).
28. Juul, A., Scheike, T., Davidsen, M., Gyllenborg, J. & Jorgensen, T. Low serum insulin-like growth factor-1 is associated with increased risk of ischemic heart disease: a population-based case-control study. *Circulation* **106**, 939–944 (2002).
29. Vasan, R. S. *et al.* Serum insulin-like growth factor I and risk for heart failure in elderly individuals without a previous myocardial infaction: the Framingham Heart Study. *Ann. Intern. Med.* **139**, 642–648 (2003).
30. Harrela, M. *et al.* Genetic and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. *J. Clin. Invest.* **98**, 2612–2615 (1996).
A twin study analysing genetic and non-genetic contributions to inter-individual variation in IGF1 levels.
31. Le Marchand, L. *et al.* Association of a common polymorphism in the human *GH1* gene with colorectal neoplasia. *J. Natl Cancer Inst.* **94**, 454–460 (2002).
32. Johnston, L. B. *et al.* Association between insulin-like growth factor 1 (IGF-1) polymorphisms, circulating IGF-1, and pre- and postnatal growth in two European small for gestational age populations. *J. Clin. Endocrinol. Metab.* **88**, 4805–4810 (2003).
33. Deal, C. *et al.* Novel promoter polymorphism in insulin-like growth factor-binding protein-3: correlation with serum levels and interaction with known regulators. *J. Clin. Endocrinol. Metab.* **86**, 1274–1280 (2001).
34. Bonafe, M. *et al.* Polymorphic variants of insulin-like growth factor I (IGF-I) receptor and phosphoinositide 3-kinase genes affect IGF-I plasma levels and human longevity: cues for an evolutionarily conserved mechanism of life span control. *J. Clin. Endocrinol. Metab.* **88**, 3299–3304 (2003).
35. Laron, Z. Prismatic cases: Laron syndrome (primary growth hormone resistance) from patient to laboratory to patient. *J. Clin. Endocrinol. Metab.* **80**, 1526–1531 (1995).
36. Maheshwari, H. G., Silverman, B. L., Dupuis, J. & Baumann, G. Phenotype and genetic analysis of a syndrome caused by an inactivating mutation in the growth hormone-releasing hormone receptor: Dwarfism of Sindh. *J. Clin. Endocrinol. Metab.* **83**, 4065–4074 (1998).
37. Wang, L. *et al.* Insulin-like growth factor-binding protein-3 gene-202 A/C polymorphism is correlated with advanced disease status in prostate cancer. *Cancer Res.* **63**, 4407–4411 (2003).
38. Schernhammer, E. S., Hankinson, S. E., Hunter, D. J., Blouin, M.-J. & Pollak, M. N. Polymorphic variation at the-202 locus in IGFBP3: influence on serum levels of insulin-like growth factors, interaction with plasma retinol and vitamin D and breast cancer risk. *Int. J. Cancer* **107**, 60–64 (2003).
39. Cheng, I. C. *et al.* Haplotype variation in insulin-like growth factor I (IGF–I) and prostate cancer risk: The multiethnic cohort. *Proc. Am. Assoc. Cancer Res.* **45**, A4505 (2004).
40. Houghton, P. J. & Huang, S. mTOR as a target for cancer therapy. *Curr. Top. Microbiol. Immunol.* **279**, 339–359 (2004).
41. Dunn, S. E. *et al.* Dietary restriction reduces IGF-I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53 deficient mice. *Cancer Res.* **57**, 4667–4672 (1997).
Provides evidence that the well-known protective effect of calorific restriction against chemical carcinogenesis in rodents is related to the IGF1-lowering effect of calorific restriction.
42. Holmes, M. D., Pollak, M. N., Willett, W. C. & Hankinson, S. E. Dietary correlates of plasma insulin-like growth factor-I and insulin-like growth factor binding protein-3 concentrations. *Cancer Epidemiol. Biomarkers Prev.* **11**, 852–861 (2002).
43. Giovannucci, E. *et al.* Nutritional predictors of insulin-like growth factor-I and their relationships to cancer in men. *Cancer Epidemiol. Biomarkers Prev.* **12**, 84–89 (2003).
44. Heaney, R. *et al.* Dietary changes favorably affect bone remodeling in older adults. *J. Am. Diet. Assoc.* **99**, 1228–1233 (1999).
45. Gunnell, D. *et al.* Are diet-prostate cancer associations mediated by the IGF axis? A cross-sectional analysis of diet, IGF-I and IGFBP-3 in healthy middle-aged men. *Br. J. Cancer* **88**, 1682–1686 (2003).
46. Chan, J. M. *et al.* Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study. *Am. J. Clin. Nutr.* **74**, 549–554 (2001).
47. Pollak, M. *et al.* Effect of tamoxifen on serum insulin-like growth factor I levels in stage I breast cancer patients. *J. Natl Cancer Inst.* **82**, 1693–1697 (1990).
48. Helle, S. I. *et al.* Alterations in the insulin-like growth factor system during treatment with diethylstillboestrol in patients with metastatic breast cancer. *Br. J. Cancer* **85**, 147–151 (2001).
49. Jernstrom, H. *et al.* Genetic and non-genetic factors associated with variation of plasma levels of insulin-like growth factor-I and insulin-like growth factor binding protein-3 in healthy premenopausal women. *Cancer Epidemiol. Biomarkers Prev.* **10**, 377–384 (2001).
50. Yee, D. & Lee, A. V. Crosstalk between the insulin-like growth factors and estrogens in breast cancer. *J. Mammary Gland Biol. Neoplasia* **5**, 107–115 (2000).
51. Song, R. *et al.* The role of Shc and insulin-like growth factor 1 receptor in mediating the translocation of estrogen receptor receptor alpha to the plasma membrane. *Proc. Natl Acad. Sci. USA* **101**, 2076–2081 (2004).
52. Abuzzahab, M. J. *et al.* IGF-1 receptor mutations resulting in intrauterine and postnatal growth retardation. *N. Engl. J. Med.* **349**, 2211–2222 (2003).
53. Lawlor, D. A., Okasha, M., Gunnell, D., Smith, G. D. & Ebrahim, S. Associations of adult measures of childhood growth with breast cancer: findings from the British Women's Heart and Health Study. *Br. J. Cancer* **89**, 81–87 (2003).
54. Mellemkjaer, L. *et al.* Birth weight and risk of early-onset breast cancer (Denmark). *Cancer Causes Control* **14**, 61–64 (2003).
55. Engeland, A., Tretli, S. & Bjorge, T. Height, body mass index, and prostate cancer: a follow-up of 950000 Norwegian men. *Br. J. Cancer* **89**, 1237–1242 (2003).
56. Gunnell, D. *et al.* Height, leg length, and cancer risk: a systematic review. *Epidemiol. Rev.* **23**, 313–342 (2001).
57. Juul, A. *et al.* The ratio between serum levels of insulin-like growth factor (IGF)-1 and the IGF binding proteins (IGFBP)-1, 2 and 3 decreases with age in healthy adults and is increased in acromegalic patients. *Clin. Endocrinol.* **41**, 85–93 (1994).
58. Stavola, B. L. *et al.* Birthweight, childhood growth and risk of breast cancer in British cohort. *Br. J. Cancer* **83**, 964–968 (2000).
59. McCormack, V. A. *et al.* Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. *Br. Med. J*. **326**, 248 (2003).
60. Sandhu, M. S., Luben, R., Day, N. E. & Khaw, K. T. Self-reported birth weight and subsequent risk of colorectal cancer. *Cancer Epidemiol. Biomarkers Prev.* **11**, 935–938 (2002).
61. Tibblin, G., Eriksson, M., Cnattingius, S. & Ekbom, A. High birthweight as a predictor of prostate cancer risk. *Epidemiology* **6**, 423–424 (1995).
62. Von Behren, J. & Reynolds, P. Birth characteristics and brain cancers in young children. *Int. J. Epidemiol.* **32**, 248–256 (2003).
63. Vatten, L. J., Nilsen, S. T., Odegard, R. A., Romundstad, P. R. & Austgulen, R. Insulin-like growth factor-I and leptin in umbilical cord plasma and infant birth size at term. *Pediatrics* **109**, 1131–1135 (2002).
64. Altinkaynak, K., Aksoy, H. H., Bakan, E. & Kumtepe, Y. Serum IGF-I and IGFBP-3 in healthy pregnancies and patients with preeclampsia. *Clin. Biochem.* **36**, 221–223 (2003).
65. Vatten, L. J., Romundstad, P. R., Trichopoulos, D. & Skjaerven, R. Pre-eclampsia in pregnancy and subsequent risk for breast cancer. *Br. J. Cancer* **87**, 971–973 (2002).
66. Boyd, N. F. *et al.* The association of breast mitogens with mammographic densities. *Br. J. Cancer* **87**, 876–882 (2002).
67. Byrne, C. *et al.* Plasma insulin-like growth factor-I, insulin-like growth factor-binding protein-3 and mammographic density. *Cancer Res.* **60**, 3744–3748 (2000).
Early report relating circulating IGF1 and IGFBP3 levels to mammographic density, a recognized breast cancer risk factor.
68. Maskarinec, G., William, A. E. & Kaaks, R. A cross-sectional investigation of breast density and insulin–like growth factor 1. *Int. J. Cancer* **107**, 996 (2003).
69. Platz, E. A. *et al.* Racial variation in insulin-like growth factor-I and binding protein-3 concentrations in middle-age men. *Cancer Epidemiol Biomarkers Prev.* **8**, 1107–1110 (1999).
70. Jernstrom, H. *et al.* Genetic factors related to racial variation in plasma levels of insulin-like growth factor-I: implications for pre-menopausal breast cancer risk. *Mol. Genet. Metab.* **72**, 144–154 (2001).
71. DeLellis, K. *et al.* IGF1 genotype, mean plasma level and breast cancer risk in the Hawaii/Los Angeles multiethnic cohort. *Br. J. Cancer* **88**, 277–282 (2003).
72. Renehan, A. G. *et al.* Acromegaly and colorectal cancer: a comprehensive review of epidemiology, biological mechanisms, and clinical implications. *Horm. Metab. Res.* **36**, 70–71 (2004).
73. Colao, A., Ferone, D., Marzullo, P. & Lombardi, G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endo. Rev.* **25**, 102–152 (2004).
74. Pollak, M., Beamer, W. & Zhang, J. C. Insulin-like growth factors and prostate cancer. *Cancer Metastasis Rev.* **17**, 383–390 (1999).

75. Yu, H. & Rohan, T. Role of the insulin-like growth factor family in cancer development and progression. *J. Natl Cancer Inst.* **92**, 1472–1489 (2000).
76. Renehan, A. G. *et al.* Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* **363**, 1346–1353 (2004).
A comprehensive review of population studies concerning IGF1 levels and cancer risk.
77. Lukanova, A. *et al.* Circulating levels of insulin-like growth factor-1 and risk of ovarian cancer. *Int. J. Cancer* **101**, 549–554 (2002).
78. Zhao, H. *et al.* Plasma levels of insulin-like growth factor-1 and binding protein-3, and their association with bladder cancer risk. *J. Urol.* **169**, 714–717 (2003).
79. Wu, X. *et al.* Serum levels of insulin-like growth factor I and risk of squamous intraepithelial lesions of the cervix. *Clin. Cancer Res.* **9**, 3356–3361 (2003).
80. Stampfer, M. J., Sacks, F. M., Salvini, S., Willett, W. C. & Hennekens, C. H. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N. Engl. J. Med.* **325**, 373–381 (1991).
81. Stampfer, M. J. The study of cancer risks in populations. *Growth Horm. IGF Res.* **10** (Suppl. A), 4–5 (2000).
82. Chan, J. M. *et al.* Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* **279**, 563–566 (1998).
A key early prospective study of circulating IGF1 levels in the context of subsequent cancer risk.
83. Spitz, M. R. *et al.* Serum insulin-like growth factor (IGF) and IGF-binding protein levels and risk of lung cancer. A case-control study nested in the β-carotene and retinol efficacy trial cohort. *Cancer Epidemiol. Biomarkers Prev.* **11**, 1413–1418 (2002).
84. Woodson, K. *et al.* Serum insulin-like growth factor I: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. *Cancer Res.* **63**, 3991–3994 (2003).
85. Pollak, M., Blouin, M. J., Zhang, J. C. & Kopchick, J. J. Reduced mammary gland carcinogenesis in transgenic mice expressing a growth hormone anatgonist. *Br. J. Cancer* **85**, 428–430 (2001).
86. Wu, Y. *et al.* Reduced circulating insulin-like growth factor I levels delay the onset of chemically and genetically induced mammary tumors. *Cancer Res.* **63**, 4384–4388 (2003).
An important example of laboratory models that provide data consistent with epidemiological research relating circulating IGF1 levels to cancer risk.
87. Majeed, N., Kaplan, P., Blouin, M.-J., Greenberg, N. & Pollak, M. *Lit* is the first germ-line mutation to reduce prostate cancer risk and prolong survival in the TRAMP transgenic model. *Proc. Am. Assoc. Cancer Res.* **44**, 877 (2003).
88. DiGiovanni, J. *et al.* Deregulated expression of insulin-like growth factor 1 in prostate epithelium leads to neoplasia in transgenic mice. *Proc. Natl Acad. Sci. USA* **97**, 3455–3460 (2000).
89. Lu, S. & Archer, M. C. Insulin-like growth factor binding protein-1 over-expression in transgenic mice inhibits hepatic preneoplasia. *Mol. Carcinog.* **36**, 142–146 (2003).
90. Eigenmann, J. E., Amador, A. & Patterson, D. F. Insulin-like growth factor I levels in proportionate dogs, chondrodystrophic dogs and in giant dogs. *Acta Endocrinol.* **118**, 105–108 (1988).
91. Withrow, S. J., Powers, B. E., Straw, R. C. & Wilkins, R. M. Comparative aspects of osteosarcoma. Dog versus man. *Clin. Orthop.* **270**, 159–168 (1991).
92. Cohen, S. M. & Ellwein, L. B. Cell proliferation in carcinogenesis. *Science* **249**, 1007–1011 (1990).
93. Sakr, W., Haas, G., Cassin, B., Pontes, J. & Crissman, J. The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients. *J. Urol.* **150**, 379–385 (1993).
94. Pollak, M. & Foulkes, W. D. Challenges to cancer control by screening. *Nature Rev. Cancer* **3**, 297–303 (2003).
95. Pollak, M., Perdue, J. F., Margolese, R. G., Baer, K. & Richard, M. Presence of somatomedin receptors on primary human breast and colon carcinomas. *Cancer Lett.* **38**, 223–230 (1987).
96. Arteaga, C. L. *et al.* Blockade of the type I somatomedin receptor inhibits growth of human breast cancer cells in athymic mice. *J. Clin. Invest.* **84**, 1418–1423 (1989).
First report of an *in vivo* model showing antineoplastic activity of an antibody that blocks the IGF1 receptor.
97. Surmacz, E. Growth factor receptors as therapeutic targets: strategies to inhibit the insulin-like growth factor-I receptor. *Oncogene* **22**, 6589–6597 (2003).
98. Wang, Y. & Sun, Y. Insulin-like growth factor receptor-1 as an anti-cancer target: blocking transformation and inducing apoptosis. *Curr. Cancer Drug Targets* **2**, 191–207 (2002).
99. Yang, X. F., Beamer, W., Huynh, H. T. & Pollak, M. Reduced growth of human breast cancer xenografts in hosts homozygous for the *'lit'* mutation. *Cancer Res.* **56**, 1509–1511 (1996).
100. Pollak, M., Polychronakos, C. & Richard, M. Insulin like growth factor 1: a potent mitogen for human osteogenic sarcoma. *J. Natl Cancer Inst.* **82**, 301–305 (1990).
101. Maloney, E. K. *et al.* An anti-insulin-like growth factor-I receptor antibody that is a potent inhibitor of cancer cell proliferation. *Cancer Res.* **63**, 5073–5083 (2003).
102. Burtrum, D. *et al.* A fully human monoclonal antibody to the insulin-like growth factor-I receptor blocks ligand-dependent signaling and inhibits human tumor growth *in vivo*. *Cancer Res.* **63**, 8912–8921 (2003).
103. Bohula, E. A. *et al.* The efficacy of small interfering RNA's targeted to the type 1 insulin-like growth factor receptor (IGF1R) is influenced by secondary structure in the IGF1R transcript. *J. Biol. Chem.* **278**, 15991–15997 (2003).
104. Sachdev, D., Hartell, J. S., Lee, A. V., Zhang, X. & Yee, D. A dominant negative type I insulin–like growth factor receptor inhibits metastasis of human cancer cells. *J. Biol. Chem.* **279**, 5017–5024 (2004).
105. Lee, C. T. *et al.* Recombinant adenoviruses expressing dominant negative insulin-like growth factor-I receptor demonstrate antitumor effects on lung cancer. *Cancer Gene Ther.* **10**, 57–63 (2003).
106. Min, Y. *et al.* Genetic blockade of the insulin-like growth factor-I receptor: a promising strategy for human pancreatic cancer. *Cancer Res.* **63**, 6432–6441 (2003).
107. Garcia-Echeverria, C. *et al. In vivo* anti-tumor activity of NVP-AEW541- A novel, potent and selective inhibitor of the IGF-IR kinase. *Cancer Cell* **5**, 231–239 (2004).
108. Mitsiades, C. S. *et al.* Inhibition of the insulin-like growth factor receptor-1 tyrosine kinase activity as a therapeutic strategy for multiple myeloma, other hematologic malignancies, and solid tumors. *Cancer Cell* **5**, 221–230 (2004).
Description of antineoplastic effects of a small-molecule inhibitor of IGF1 receptor kinase activity.
109. Girnita, A. *et al.* Cyclolignans as inhibitors of the insulin-like growth factor-1 receptor and malignant cell growth. *Cancer Res.* **64**, 236–42 (2004).
110. Mamane, Y. *et al.* eIF4E — from translation to transformation. *Oncogene* **23**, 3172–3179 (2004).
111. Bjornsti, M.-A. & Houghton, P. J. The TOR pathway: a target for cancer therapy. *Nature Rev. Cancer* **4**, 335–348 (2004).
112. Wendel, H.-G. *et al.* Survival signalling by Akt and eIF4E in oncogenesis and cancer therapy. *Nature* **428**, 332–337 (2004).
113. Pollak, M. & Schally, A. V. Mechanism of antineoplastic action of somatostatin analogues. *Proc. Soc. Exp. Med. Biol.* **217**, 143–152 (1998).
114. Szereday, Z. *et al.* Antagonists of growth hormone-releasing hormone inhibit the proliferation of experimental non-small cell lung carcinoma. *Cancer Res.* **63**, 7913–7919 (2003).
115. Kopchick, J. J., Parkinson, C., Stevens, E. C. & Trainer, P. J. Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. *Endocr. Rev.* **23**, 623–646 (2002).
116. Ingle, J. *et al.* A randomized trial of tamoxifen alone or combined with octreotide in the treatment of women with metastatic breast cancer. *Cancer* **85**, 1284–1292 (1999).
117. Sell, C. *et al.* Effect of a null mutation of the insulin-like growth factor I receptor gene on growth and transformation of mouse embryo fibroblasts. *Mol. Cell. Biol.* **14**, 3604–3612 (1994).
118. LeRoith, D. & Roberts, C. T. Jr. The insulin-like growth factor system and cancer. *Cancer Lett.* **195**, 127–137 (2003).
119. Lu, Y., Zi, X., Zhao, Y., Mascarenhas, D. & Pollak, M. Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). *J. Natl Cancer Inst.* **93**, 1852–1857 (2001).
Provides evidence that the efficacy of ERBB2-targeting therapies is maximized when IGF1R signalling is reduced.
120. Camirand, A. & Pollak, M. Co-targeting IGF-1R and c-kit: synergistic inhibition of proliferation and induction of apoptosis in H 209 small cell lung cancer cells. *Br. J. Cancer* 20 April 2004 (doi:10.1038/sj.bjc.6601682).
121. Pandini, G. *et al.* Insulin/insulin-like growth factor-I hybrid receptors have different biological characteristics depending on the insulin receptor isoform involved. *J. Biol. Chem.* **277**, 39684–39695 (2002).
122. Lynch, T. H. *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to Gefitinib. *N. Engl. J. Med.* **350**, 1–11 (2004).
123. Baselga, J. *et al.* Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J. Clin. Oncol.* **20**, 4292–4302 (2002).
124. Oh, J. S. *et al.* Insulin-like growth factor-1 inscribes a gene expression profile for angiogenic factors and cancer progression in breast epithelial cells. *Neoplasia* **4**, 204–217 (2002).
125. Ng, S. T. *et al.* Growth hormone treatment induces mammary gland hyperplasia in aging primates. *Nature Med.* **3**, 1141–1144 (1997).
Shows a relation between IGF1 levels in the circulation and cellular proliferation in the mammary gland.
126. Lukanova, A. *et al.* Prediagnostic levels of C-peptide, IGF-I, IGFBP-1,-2 and-3 and risk of endometrial cancer. *Int. J. Cancer* **108**, 262–268 (2004).
127. Muti, P. *et al.* Fasting glucose is a risk factor for breast cancer: a prospective study. *Cancer Epidemiol. Biomarkers Prev.* **11**, 1361–1368 (2002).
128. Hsing, A. W., Gao, Y. T., Chua, S. Jr., Deng, J. & Stanczyk, F. Z. Insulin-resistance and prostate cancer risk. *J. Natl Cancer Inst.* **95**, 67–71 (2003).
129. Kaaks, R. *et al.* Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J. Natl Cancer Inst.* **92**, 1592–1600 (2000).
130. Goodwin, P. J. *et al.* Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J. Clin. Oncol.* **20**, 42–51 (2002).
131. Amiling, C. L. *et al.* Pathologic variables and recurrance rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. *J. Clin. Oncol.* **22**, 439–445 (2004).
132. Haffner, S. & Taegtmeyer, H. Epidemic obesity and the metabolic syndrome. *Circulation* **108**, 1552–1553 (2003).
133. Padez, C. Stature and stature distribution in Portuguese male adults 1904–1998: the role of environmental factors. *Am. J. Human Biol.* **14**, 39–49 (2002).
134. Deapen, D., Liu, L., Perkins, C., Bernstein, L. & Ross, R. K. Rapidly rising breast cancer incidence rates amoung Asian-American women. *Int. J. Cancer* **99**, 747–750 (2002).
135. Valerianova, Z., Gill, C., Duffy, S. W. & Danon, S. E. Trends in incidence of various cancers in Bulgaria, 1981–1990. *Int. J. Epidemiol.* **23**, 1117–1126 (1994).
136. You, W. C. *et al.* Rapid increase in colorectal cancer rates in urban Shanghai, 1972–97, in relation to dietary changes. *J. Cancer Epidemiol. Prev.* **7**, 143–146 (2002).
137. Giovannucci, E. & Pollak, M. Risk of cancer after growth-hormone treatment. (editorial). *Lancet* **360**, 268–269 (2002).
138. Rudman, D. *et al.* Effects of Human Growth Hormone in Men Over 60 Years Old. *N. Engl. J. Med.* **323**, 1–6 (1990).
139. Vance, M. L. Can human growth hormone prevent aging? *N. Engl. J. Med.* **348**, 779–780 (2003).
A critical reassessment of the putative 'anti-ageing' effects of GH administration.
140. Wetterau, L. & Cohen, P. Role of insulin-like growth factor monitoring in optimizing growth hormone therapy. *J. Pediatr. Endocrinol. Metab.* **13**, 1371–1376 (2000).
141. Swerdlow, A. J., Higgins, C. D., Adlard, P. & Preece, M. A. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959–85: a cohort study. *Lancet* **360**, 273–277 (2002).
142. Flurkey, K., Papaconstantinou, J., Miller, R. A. & Harrison, D. E. Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. *Proc. Natl Acad. Sci. USA* **98**, 6736–6741 (2001).
143. Holzenberger, M. *et al.* IGF-I receptor regulates lifespan and resistance to oxidative stress in mice. *Nature* **421**, 182–187 (2003).
144. Tyner, S. D. *et al.* p53 mutant mice that display early ageing-associated phenotypes. *Nature* **415**, 45–53 (2002).
145. Maier, B. *et al.* Modulation of mammalian life span by the short isoform of p53. *Genes Dev.* **18**, 306–319 (2004).
146. Cats, A. *et al.* Increased epithelial cell proliferation in the colon of patients with acromegaly. *Cancer Res.* **56**, 523–526 (1996).
147. Miller, R. A., Harper, J. M., Galecki, A. & Burke, D. T. Big mice die young: early life body weight predicts longevity in genetically heterogenous mice. *Aging Cell* **1**, 22–29 (2002).
148. Ma, J. *et al.* Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I, and IGF-binding protein-3. *J. Natl Cancer Inst.* **91**, 620–625 (1999).
149. Giovannucci, E. *et al.* A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. *Cancer Epidemiol. Biomarkers Prev.* **9**, 345–349 (2000).

150. Palmqvist, R. *et al.* Plasma insulin-like growth factor-1, insulin-like growth factor binding protein-3, and risk of colorectal cancer: a prospective study in northern Sweden. *Gut* **50**, 642–646 (2002).
151. Probst-Hensch, N. M. *et al.* IGF-1, IGF-2 and IGFBP-3 in prediagnostic serum: association with colorectal cancer in a cohort of Chinese men in Shanghai. *Br. J. Cancer* **85**, 1695–1699 (2001).
152. Chan, J. M. *et al.* Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. *J. Natl Cancer Inst.* **94**, 1099–1106 (2002).
153. Harman, S. M., Metter, E. J., Blackman, M. R., Landis, P. K. & Carter, H. B. Serum levels of insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-3, and prostate-specific antigen as predictors of clinical prostate cancer. *J. Clin. Endocrinol. Metab.* **85**, 4258–4265 (2000).
154. Stattin, P. *et al.* Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. *J. Natl Cancer Inst.* **92**, 1910–1917 (2000).
155. Lacey, J. V. J. *et al.* Null association between insulin-like growth factors, insulin-like growth factor-binding proteins, and prostate cancer in a prospective study. *Cancer Epidemiol. Biomarkers Prev.* **10**, 1101–1102 (2001).
156. Hankinson, S. E. *et al.* Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet* **351**, 1393–1396 (1998).
157. Toniolo, P. *et al.* Serum insulin-like growth factor-I and breast cancer. *Int. J. Cancer* **88**, 828–832 (2000).
158. Kaaks, R. *et al.* Prospective study of IGF-I, IGF-binding proteins, and breast cancer risk, in northern and southern Sweden. *Cancer Causes Control* **13**, 307–316 (2002).
159. Krajcik, R. A., Borofsky, N. D., Massardo, S. & Orentreich, N. Insulin-like gorwth factor (IGF-I), IGF-binding proteins, and breast cancer. *Cancer Epidemiol. Biomarkers Prev.* **11**, 1566–1573 (2002).
160. Keinan-Boker, L. *et al.* Circulating levels of insulin-like growth factor-I, its binding proteins 1-2-3, C-peptide, and risk of postmenopausal breast cancer. *Int. J. Cancer* **106**, 90–95 (2002).
161. Wakai, K. *et al.* Serum insulin-like growth factors, insulin-like growth factor-binding protein-3, and risk of lung cancer death: a case-control study nested in the Japan Collaborative Cohort (JACC) Study. *Jpn. J. Cancer Res.* **93**, 1279–1286 (2002).
162. London, S. J. *et al.* Insulin-like growth factor I, IGF-binding protein 3, and lung cancer risk in a prospective study of men in China. *J. Natl Cancer Inst.* **94**, 749–754 (2002).
163. Lukanova, A. *et al.* A prospective study of insulin-like growth factor-I, IGF-binding proteins-1,-2 and -3 and lung cancer risk in women. *Int. J. Cancer* **15**, 888–892 (2001).
164. Jackson-Booth, P. G., Terry, C., Lackey, B., Lopaczynska, M. & Nissley P. Inhibition of the biologic response to insulin-like growth factor I in MCF-7 breast cancer cells by a new monoclonal antibody to the insulin-like growth factor-I receptor. The importance of receptor down-regulation. *Horm. Metab. Res.* **35**, 850–856 (2003).
165. Majumder, P. K. *et al.* mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways. *Nature Med.* **10**, 594–601 (2004).
166. George, S. *et al.* A family with severe insulin resistance and diabetes due to a mutation in AKT2. *Science* **304**, 1325–1328 (2004).

Acknowledgements

The authors are grateful for helpful comments from the anonymous reviewers and the editors. We apologize to colleagues whose contributions could not be cited due to space constraints.

Competing interests statement

The authors declare competing financial interests: see web version for details.