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Focus On

IGF-I, IGF-binding protein-3 and breast cancer risk

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Abstract Insulin-like growth factor I (IGF-I) and its main binding protein 3 (IGFBP-3) are multi-regulatory peptides important in tumour cell growth and survival. In the circulation, they occur in large quantities and are readily measured. Across a population, concentrations vary and this may impact on risk of cancers common in western societies. Emerging epidemiological evidence supports the notion that higher levels of IGF-I are associated with increased risk of pre-menopausal, but not post-menopausal, breast cancer. Higher levels of IGFBP-3 may also predict for increased risk of pre-menopausal breast cancer, but this is contrary to the conventional view that this peptide is tumour protective. Nutritional and lifestyle factors, important in breast cancer risk, also inter-relate with circulating levels of IGF-I, but in many circumstances, the relationships are complex. It is becoming increasingly important that the clinical breast oncologist understands the physiology of the IGF system and its potential role in cancer risk assessment and prevention.

Keywords: Insulin-like growth factor; Breast cancer risk; Cancer prevention; Systematic review; Tumorogenesis; Peptides

Introduction

Insulin-like growth factor I (IGF-I) and its main binding protein 3 (IGFBP-3), are both growth hormone (GH) dependent regulatory peptides, and together are referred to as the *GH–IGF-I axis* [1]. Both peptides are involved in cell growth and survival, and thus, have been implicated in tumour development [2]. Unlike many other growth factors, they exhibit both classical hormonal characteristics and local tissue influences, occur in large quantities in the circulation, and are readily measured. There are wide inter-individual variations in IGF-I and IGFBP-3 concentrations, and it is speculated that this variability may influence the distribution of cancer risk in a population [3,4]. Over recent years, there has been mounting evidence supporting the hypothesis that circulating levels of IGF-I and IGFBP-3 influence development of common cancers within western societies, of which breast cancer is well documented.

This review will focus on the epidemiological evidence linking circulating IGF-I, IGFBP-3 and breast cancer risk, and highlight specific recent developments relevant to the potential role of these biomarkers in cancer risk assessment and prevention. There are several complex relationships between the IGF system and other risk factors for breast cancer such as oestrogens and hormonal replacement therapy [5], diet and energy intake [6,7], excess body weight [8,9] and physical activity [10], but these are dealt with elsewhere as referenced. The IGF physiology and biological mechanisms relevant to cancer development will be summarized, but thorough dissertations of these areas are beyond the scope of this review. The potential role of the IGF-I receptor

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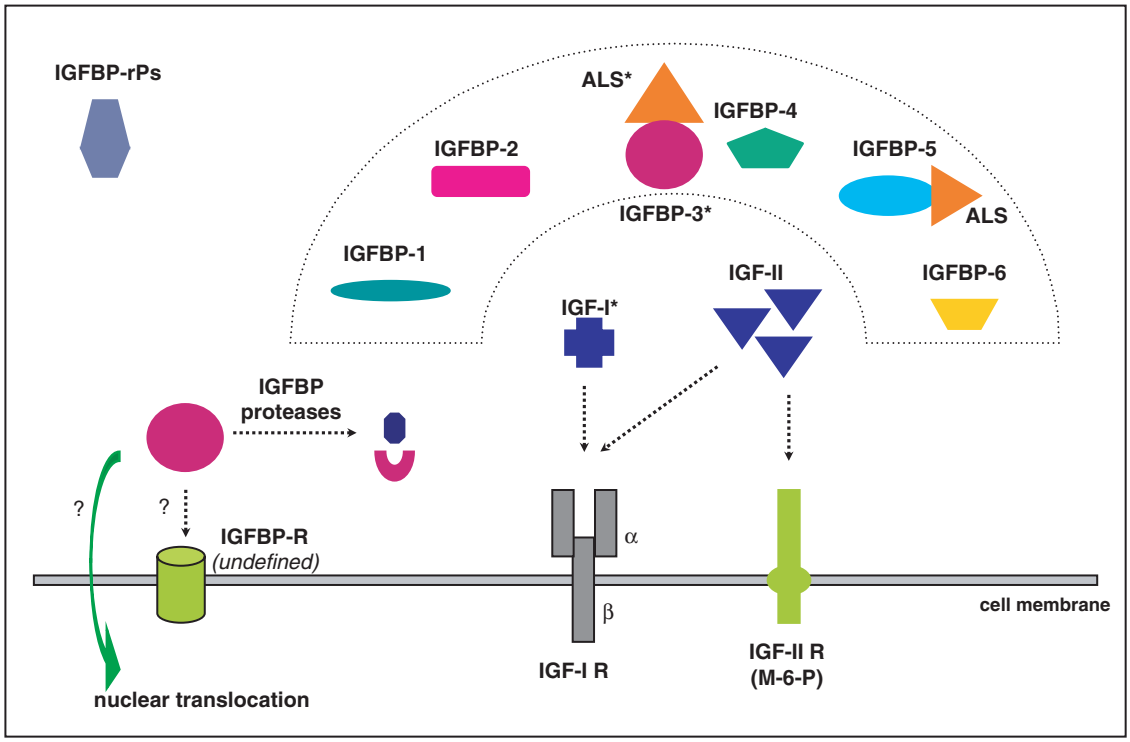

* GH-dependent

Figure 1.
Schematic diagram of the IGF system. M-6-P: mannose-6-phosphate.

as a therapeutic target is also beyond this review, and dealt with elsewhere [11,12].

Physiology of the IGF system

The IGF system is a complex molecular network which includes two ligands (IGF-I and IGF-II), two receptors (IGF-IR and IGF-IIR or mannose-6-phosphate receptor), six high-affinity-binding proteins (IGFBP-1–6), at least four low-affinity IGF binding-protein-related peptides (IGFBPrP-1–4), and several binding-protein proteases [13–15] (Fig. 1). The major form of binding protein in human circulation is IGFBP-3 [16]. Unlike the other IGF-binding proteins, IGFBP-3 is typically fully saturated, and in the human circulation, exists with the IGF ligands and an acid-labile subunit (ALS) in the form of a 150-kDa ternary complex [17]. Thus, circulating IGF-I exists in three pools: ternary complex (70–80%); a 50-kDa IGFBP pool (20–25%); and free IGF-I (<5%) [15]. Under normal conditions, total IGF-I and IGF-II, and total IGFBP-3 in serum are in equimolar concentrations [18] (Fig. 2).

IGF-I, IGF-II and the IGF-binding proteins occur in large quantities in the circulation and are readily measured. In addition to being GH dependent, IGF-I and IGFBP-3 are influenced by age (mean levels of both peptides decline with age after puberty) [19], gender (mean levels of IGF-I are higher in men; mean levels of IGFBP-3 are higher in women) [20], and nutritional status (calorie restriction is associated with profound reduction in serum IGF-I concentrations) [21].

IGF-I and IGFBP-3: biological actions and tumour development

IGF-I and IGFBP-3 may influence tumour development at many levels, and through mechanisms dependent and independent of the IGF-I receptor (IGF-IR) as summarized in Box 1.

Comprehensive reviews of the biological actions of IGF-I and IGFBP-3 in relation to tumour development can be found elsewhere [2,28,42], but are summarized here.

IGF-1 and tumorogenesis

Several cellular actions of IGF-I favour tumour growth, including mitogenesis, antiapoptosis, induction of vascular endothelial growth factor (pro-angiogenesis) and increased cell migration. In addition, IGF-I stimulates pathways key to early tumour initiation (e.g. beta-catenin) [43] and potentiates the effects of other cell growth stimulants including oestrogens [44].

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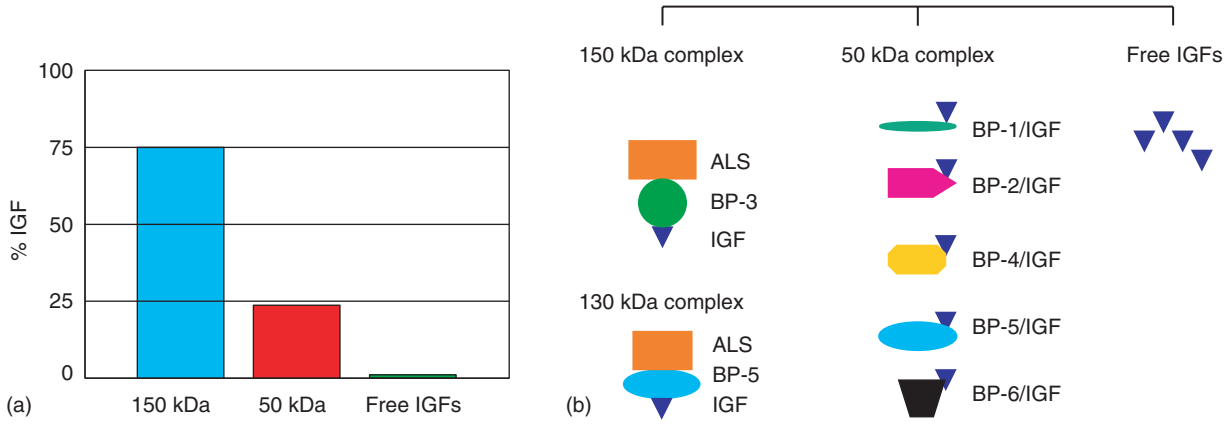

Figure 2.
The various IGF pools in human serum and IGF–IGFBP complexes. (a) The relative distribution of IGFs between 150, 50 kDa and the free pool. (b) Proposed model of the forms in which IGFs circulate in human serum. Within the complexes IGF = α-subunit, IGFBP = β-subunit and ALS = δ-subunit.

Box 1: Biological actions of IGF-I and IGFBP-3, and tumorogenesis.

	Comments
IGF-I ligand	
Mitogenesis	Almost ubiquitous action in human cells [22]
Anti-apoptosis	Potent inhibitor of apoptosis induced by gamma radiation, cytotoxic agents (e.g. etoposide) and TNF [23]
Pro-angiogenesis	Induces hypoxia-inducible factor 1-mediated VEGF production [24]
Cell migration	In cooperation with integrins and E-cadherin [25]
Cell adhesion	Beta-catenin pathway initiation [26]
Interactions with ER	Synergistic in cell proliferation [27]
IGFBP-3	
Growth inhibitory	(In theory) through high-affinity sequestration of IGF ligands [28]
Anti-proliferation	IGFBP-3 may bind IGF-I receptor and inhibit IGF-I action [29,30]
Potentiation of apoptosis	Potentiates ceramide-induced apoptosis in Hs578T breast cancer cells [31]
Anti-apoptosis	Independent of IGF-I receptor [32,33]
ECM interactions	Interacts with fibronectin [34,35] and glycosaminoglycans [36]
Interactions with signal pathways	TGF-beta signalling [33], retinoid X receptor [37] and epidermal growth factor signalling [38]
p53 interaction	p53 activation induces IGFBP-3 production [39]
Influences pro-apoptotic proteins	Modulates expression of pro-apoptotic proteins, Bax and Bcl-2 [40,41]

TNF: tumour necrosis factor; VEGF: vascular endothelial growth factor; ER: oestrogen receptor; ECM: extracellular matrix; TGF: transforming growth factor.

The effects of IGF-I are mediated through IGF-IR, a tyrosine kinase receptor. Most breast cancer cell lines (notable exception is Hs578T) express functional IGF-IRs, though unlike other cancers, IGF-IR expression is seldom increased [45,46]. IGF-IR stimulation influences signalling through other receptors such as the HER/neu receptor, thought to be important for the inhibitory effects of trastuzumab [47]. The IGF-IR signalling pathways are complex and not fully understood, and reviewed elsewhere [48,49]. The predominant mitogenic and apoptotic signalling molecule activated by oestrogen receptor (ER) positive cells is insulin receptor substrate-I (IRS-I), which activates downstream networks including phosphaditidylinositol (PI) 3 kinase and the mitogen activating protein (MAP) kinase pathways.

IGFBP-3 and tumorogenesis

At a cellular level, IGFBP-3 is multi-functional having actions that may favour and/or inhibit tumour growth [28,40]. Conventionally, co-treatment of IGF-I and the binding protein causes IGFBP-3 to inhibit IGF-mediated effects via high-affinity sequestration of the ligand, leading to the prevention of IGF-induced IGF-IR auto-phosphorylation and signalling – this is the *IGF-dependent effect*. It is becoming increasingly clear that, apart for modulation of IGF actions,

IGFBP-3 may exert intrinsic bio-activity either in the absence of IGFs (*IGF-independent effects*) or in the presence of IGFs without triggering IGF-IR signalling (*IGF-IR-independent effects*) [28]. In addition, IGFBP-3 action may be modulated through proteolytic enzymes, and in turn, the cleaved IGFBP-3 fragments may either potentiate or inhibit tumour growth [50]. Paradoxically, IGFBP-3 may also inhibit IGF-IR activation independent of IGF-I [30].

On balance, most *in vitro* studies show that IGFBP-3 is tumour inhibitory, but it is possible that in some circumstances, resistance develops to the inhibitory effects of IGFBP-3, or alternatively, a more appropriate model of *in vivo* action may be an anchorage-dependent system, in which IGFBP-3 demonstrates anti-apoptotic (tumour favouring) characteristics [34]. A further dimension is that tissue expression of IGFBP-3 in the presence of excess circulating IGFBP-3 may be organ dependent [51].

Epidemiological studies

In 1998, in a seminal paper from the Health Professional's study, Chan *et al*. showed that IGF-I levels in prospectively collected plasma positively predicted, while IGFBP-3 levels negatively predicted for the development of prostate cancer [52]. Further studies on breast [53], colorectal [54], and lung [55] cancer risk substantiated these observations, and a hypothesis emerged that circulating IGF-I levels are positively associated, whereas IGFBP-3 levels are inversely associated with cancer risk. However, the results from some studies were inconsistent, and the present authors felt that there was a need for a better understanding of the reasons underlying heterogeneous results, including differences between cancer sites, study populations and designs, and assay characteristics. We addressed these questions in a systematic review and meta-regression analysis published recently in the *Lancet* [56]. A summary of this comprehensive analysis and its potential implications are the focus of the remainder of this review.

Systematic review and meta-regression analysis

Our systematic review [56] was conducted using Cochrane methodology and reported in accordance with QUORUM recommendations [57]. In particular, the search (to December 2002), inclusion criteria and sub-group analyses were performed based on a pre-study protocol and *a priori* hypotheses. In addition, sensitivity analyses were performed at several levels (mainly using meta-regression methods) to explore for sources of heterogeneity and confounding. We considered cohort and case-control studies if they reported analyses of the relationships between measurements of circulating IGF-I and/or IGFBP-3 and invasive cancer. For breast cancer, the analysis considered pre- and post-menopausal breast cancers separately, excluding reports on 'all invasive breast cancers'.

Six studies [53,58–62] on breast cancer fulfilled inclusion criteria (Table 1). In meta-analyses performed – using random-effects methods [63] – comparing uppermost vs. lowermost categories, IGF-I was associated with pre-menopausal (odds ratio (OR) = 1.93, 95% confidence interval (CI): 1.38–2.69, $P < 0.001$) but not post-menopausal breast cancer (Table 2). The analysis for IGFBP-3 was based on five studies, as the study of Hankinson *et al*. [53] did not report associations for IGFBP-3. Comparing uppermost vs. lowermost categories, IGFBP-3 was positively and significantly associated with pre-menopausal breast cancer (OR = 1.93, 95% CI: 1.28–2.99, $P = 0.002$).

We recognized that studies differed in reporting risk using different categories (tertiles to quartiles). To address this, we calculated study-specific dose–response slopes incorporating data between

Table 1. Characteristics of the six breast cancer studies meeting inclusion criteria*.

Authors	Country	Study design	Case/control	Sample medium	IGF-I measurements	IGFBP-3 measurements
Del Giudice *et al*. [58]	Canada	Hosp c/c PRM only	99/99	Plasma, NOS	RIA (Nic)	RIA (DSL)
Hankinson *et al*. [53]	USA	Nested c/c PRM/PSM	397/620	HP	ELISA (DSL)	ELISA (DSL)
Toniolo *et al*. [60]	USA	Nested c/c PRM/PSM	287/706	Serum	RIA after AC	RIA (in-house)
Yu *et al*. [61]	China	Pop c/c PRM/PSM	300/300	EDTA/HP	ELISA (DSL)	ELISA (DSL)
Muti *et al*. [62]	Italy	Nested c/c PRM/PSM	133/503	Serum	IRMA (DSL)	IRMA (DSL)
Krajcik *et al*. [59]	USA	Nested c/c PRM/PSM	126/126	Serum	RIA (Nic)	IRMA (DSL)

*For analysis inclusion, studies had to fulfil three criteria: (i) published as a full article, (ii) findings expressed as OR with 95% CI, (iii) association reported for at least three categories (tertiles to quintiles) of peptide levels. c/c: case-control design; PRM: pre-menopausal; PSM: post-menopausal; HP: heparin plasma sampling; EP: EDTA (ethylene diamine tetra-acetic acid) plasma; NOS: not otherwise specified; ELISA: enzyme-linked immunoabsorbant assay; IRMA: immunoradiometric assay; RIA: radioimmunassay; AC: acid chromatography; DSL: Diagnostic Systems Laboratories, TX; NIC: Nichols Institute, CA.

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the lowermost and uppermost categories. These were calculated by relating the natural log of OR for different exposure levels to the reported blood concentrations (normalized to a percentile scale) using a previously described method [64]. A linear relationship between exposure and risk was assumed. The dose–response analysis confirmed that increasing IGF-I concentrations were associated with the risk of pre-menopausal breast cancer ($P < 0.001$) (Table 3). Similarly, an association between IGFBP-3 levels and pre-menopausal breast cancer was found ($P = 0.05$). The sizes of association for each cancer site were similar to those estimated in the baseline meta-analyses, suggesting that the assumption of linearity for the dose–response analysis was valid.

We undertook several sensitivity analyses, and with particular relevance to breast cancer, we addressed whether the inclusion criteria affected results. Specifically, our criteria excluded the large study on breast cancer risk by Kaaks *et al*. [65], as the analysis was based on a non-clinical definition of menopausal status, contrasting with the included breast cancer studies. When this study was included [65], the results were not materially altered.

In the correspondence arising out of this paper, Holly pointed out that menopausal status in the breast cancer studies was defined at the time of blood collection, and that some women categorized as 'pre-menopausal' breast cancer may indeed have been women sampled in pre-menopausal status, but their cancers occurred in the post-menopausal period [66]. This raises two interesting issues:

1. If there is truly no association between IGF-I, IGFBP-3 and post-menopausal breast cancer, then contamination of this group by 'pre-menopausal' women would tend to attenuate reported increased OR for pre-menopausal breast cancer.
2. Alternatively, it is conceivable that pre-menopausal women with elevated concentrations of circulating IGF-I and/or IGFBP-3 retain an increased risk of cancer into the post-menopausal age period, but currently this potential effect is too small to detect.

There is a need to determine these nuisances in future studies [67].

Studies in pre-malignant breast lesions

A Greek case-control study reported that high-IGF-I and low-IGFBP-3 circulating levels are associated with pre-menopausal breast ductal carcinoma *in situ*, but sample numbers were small [68]. Two other studies addressed associations with mammographic density as a risk factor for breast cancer. Within the Nurses' Health Study, Byrne *et al*. found that mammographic density was positively associated with plasma IGF-I levels and inversely associated

Table 2. Meta-analysis: comparisons of highest vs. lowest peptide categories for circulating IGF-I and IGFBP-3.

	Number of studies	Cases/controls	Summary OR (95% CI)	*P*-value	Tests for heterogeneity
Associations with IGF-I					
Pre-menopausal breast cancer	6	660/1193	1.93 (1.38, 2.69)	<0.001	$\chi^2_5 = 2.5, P = 0.77$
Post-menopausal breast cancer	5	672/1131	0.95 (0.62, 1.33)	0.75	$\chi^2_4 = 2.7, P = 0.61$
Associations with IGFBP-3					
Pre-menopausal breast cancer	5	584/1088	1.96 (1.28, 2.99)	0.002	$\chi^2_4 = 2.5, P = 0.77$
Post-menopausal breast cancer	4	367/648	0.97 (0.53, 1.77)	0.92	$\chi^2_3 = 2.7, P = 0.61$

Random-effects method used. Data calculated with maximally adjusted OR.

Table 3. Meta-analysis of dose–response associations with circulating IGF-I and IGFBP-3.

	Number of studies	OR comparing 75th with 25th percentile (95% CI)	*P*-value
Associations with IGF-I			
Pre-menopausal breast cancer	4	1.65 (1.26, 2.08)	<0.001
Post-menopausal breast cancer	4	0.95 (0.77, 1.17)	0.63
Associations with IGFBP-3			
Pre-menopausal breast cancer	3	1.51 (1.01, 2.27)	0.05
Post-menopausal breast cancer	3	1.01 (0.74, 1.38)	0.93

Random-effects meta-regression of dose–response slopes that represent the estimates of a linear relationship between the natural logarithm of the OR and the percentile of circulation blood levels, scaled to an increase from 25th to 75th percentile.

with plasma IGFBP-3 levels among pre-menopausal but not post-menopausal women [69]. In a cross-sectional design, Maskarinec and colleagues reported that mammographic densities were not associated with IGF-I, but there was an inverse relation with IGFBP-3 and a positive association with the IGF-I/IGFBP-3 ratio among pre-menopausal women [70]. By contrast, a Canadian study has recently shown a positive trend in mean percentage of breast density by the number of A alleles of the IGFBP-3 gene among pre-menopausal women; in turn, the number of A alleles correlate with IGFBP-3 levels in the circulation [71]. Finally, a cross-sectional Swedish study noted that the serum IGF-I/IGFBP-3 and IGF-I/IGFBP-1 ratios were elevated in pre-menopausal women with type I benign breast cysts [72].

Other studies

The search strategy in the *Lancet* review was to December 2002. Since then, there have been at least a further three epidemiological studies on breast cancer risk that would fulfil inclusion criteria used in our analysis. All three studies [73–75] were in relation to post-menopausal breast cancer and concur with the *Lancet* review's findings of no association with either IGF-I or IGFBP-3 circulating levels. By contrast, a Chinese group of investigators, who previously reported a positive association between serum IGFBP-3 and pre-menopausal breast cancer risk [61], recently reported 30–60% elevated risk of pre-menopausal breast cancer associated with homozygosity for the variant allele in polymorphisms A-202C, G227C, 5606InsA, and C5827T, functional alleles generally associated with reduced mean concentrations of circulating IGFBP-3 [76].

In addition, two meta-analyses have been published subsequent to the *Lancet* review, specifically examining relationships with breast cancer risk. The review reported by Shi *et al*. [77] used less restrictive inclusion criteria and analysed 16 publications. The meta-analysis was performed using a method known as Hedges' standardized mean differences involving the calculation of weighted mean effect sizes and their 95% CIs from the reported concentrations of each peptide for each individual study. Despite these differences (and potential limitations), the findings of this review are broadly similar to our *Lancet* review – concentrations of both total IGF-I and IGFBP-3 were positively associated with pre-menopausal breast cancer risk. The meta-analysis reported by Sugumar *et al*. [78] was limited to pre-menopausal breast cancer only, and used similar selection criteria to those in our review. The authors performed their meta-analysis based on six studies, and concluded that there were marginally significant associations with IGF-I concentrations, but no associations with IGFBP-3 concentrations. We attempted to repeat these analyses and discovered that there were major discrepancies between the 95% CIs listed by Sugumar *et al*. and those stated within the individual studies. We reperformed the analyses using the correctly reported ORs and 95% CIs, and calculated very similar estimates to those reported in our *Lancet* paper [79].

The IGFBP-3 debate

One of the main areas of debate from the *Lancet* paper arises from the observation that circulating IGFBP-3 concentrations was significantly and *positively* associated with risk of pre-menopausal breast cancer (further debate can be found at www.christie.man.ac.uk/profinfo/department/surgery/default.htm.) This goes against conventional thinking because, as pointed out above, there is a large amount of experimental literature demonstrating that IGFBP-3 is anti-proliferative and pro-apoptotic, and by implication is tumour protective. However, there are two notable laboratory studies that show IGFBP-3 as potentially tumour growth enhancing. Firstly, McCaig *et al*. [34] showed that, depending on the cellular environment, IGFBP-3 may be anti-apoptotic in IGF-I independent Hs578T breast cells. Secondly, an authoritative French group of investigators have shown that IGFBP-3 may promote cell growth through direct stimulation of phosphatidylinositol 3-kinase in MCF-7 breast carcinoma cells, a signalling pathway that is mitogenic for these cells [80]. Within our analysis, the positive association between circulating IGFBP-3 concentrations and pre-menopausal breast cancer was among the most consistent with no evidence of statistical heterogeneity ($P = 0.28$), and for the present, these seem to be the best epidemiological data. A recent narrative review in *Nature Cancer Reviews* has pointed out that associations with IGFBP-3 are most inconsistent and that many issues including differences in assays, populations and other confounding factors (e.g. cigarette smoking) may be relevant [81].

Other circulating IGF peptides

A small number of studies have evaluated other components of the circulating IGF system and breast cancer risk. Li *et al*. [82] measured plasma-free IGF-I levels and found a marginally statistically significant increased risk of breast cancer (not categorized into pre- and post-menopausal status), and this association was independent of total IGF-I levels. However, this was a case-control design and the elevated levels of free IGF-I in the cases may reflect known aberrations of the circulating IGF system in women with

breast cancer, such as increased IGFBP-3 proteolysis [83,84].

Circulating IGFBP-1, which is inversely related to insulin concentrations and may be an acute regulator of IGF-I tissue levels [85], has been measured in three studies, but in all, there were no significant associations with breast cancer risk [59,65,73]. Circulating IGFBP-2, which is conventionally considered as a tumour marker [86], was measured in the above three epidemiological studies, and reported to have a significant inverse association with post-menopausal breast cancer in the Kaiser Permanente cohort [59], but not in the other two cohorts [65,73].

Lifestyle, nutrition and breast cancer prevention

IGFs are influenced by nutritional and lifestyle factors, which in turn are risk factors for many non-smoking-related cancers [87]. For the first time, our systematic review demonstrated that the associations between IGF-I, IGFBP-3 and cancer risk vary by cancer site [56]. In turn, cigarette smoking is associated with a reduction in mean serum IGFBP-3 levels, and to a lesser extent, IGF-I levels [81]. Specifically, the findings of the *Lancet* review suggest that circulating IGF-I levels are positively associated with the risk of non-smoking-related malignancies – namely, prostate, colorectal and pre-menopausal breast. These cancers are variably associated with energy-related factors such as body mass index (BMI), physical activity and growth in early life [88]. As IGF-I is an energy-related peptide, it is tempting to speculate that it is a key link between these risk factors and disease, but the relationships are complex. In adulthood, IGF-I is related to BMI in a non-linear manner – low levels in low BMI, increases thereafter with increasing BMI, but decreases again in obesity (probably due to blunted growth hormone secretion) [8]. Similarly, circulating IGF-I levels tend to be inversely related to physical activity [89,90], but the relationship may be dependent on long-term fitness status [89]. Interventional studies have reported variable relationships between physical training and IGFBP-3 concentrations [89,90]. During adolescence, circulating IGF-I levels are highly correlated with growth and body height, but are less strong in adulthood [19]. Circulating IGF-I concentrations appear unrelated to lung cancer risk, which would be predicted, as this malignancy is weakly associated with energy-related factors. Increasingly studies also show that certain dietary factors, themselves cancer risk factors, increase IGF-I levels like milk [91], increased red meat consumption [6] and zinc [92], while others like tomato juice (containing lycopene) [93] reduce IGF-I levels in the circulation. Paradoxically, soya protein, thought to be protective for breast cancer, is associated with increased levels of serum total IGF-I [94].

In addition, the GH–IGF-I axis is highly responsive to extremes of nutritional status and this may be involved as one of the underlying mechanisms through which caloric restriction may affect cancer risk [95,96]. However, across general populations, studies evaluating the relationship between total energy intake and circulating IGF peptide concentrations have reported a positive association with plasma IGF-I, and an inverse association with plasma IGFBP-3, in one US study [6], but no associations with the two peptides in cohorts from the UK [93,97], Singapore [94], Hawaii [7] and the Netherlands [98]. However of particular interest to early life events and breast cancer risk, in a group of 87 post-menopausal women, Elias *et al*. [99] found that childhood exposure to the 1944–1945 Dutch famine was associated with increased plasma levels of IGF-I and IGFBP-3, whereas IGFBP-1 and -2 levels were weakly decreased. These results are opposite to immediate responses seen under starvation and the authors hypothesize that this could indicate a permanent overshoot upon improvement of nutritional status after the famine.

A further paradox is the observation that post-menopausal breast cancer is associated with adiposity, insulin resistance and the metabolic syndrome [100], yet these same factors are risk factors for cardiovascular disease and type 2 diabetes mellitus, and in turn, the former is associated with low levels of circulating IGF-I [101,102], while the latter is predicted by a complex interaction of IGFBP-1 levels and low-IGF-I circulating concentrations [103]. It is tempting to speculate that a woman's circulating level of IGF-I may have greatest important for cancer risk prior to the menopausal, and for risk of cardiovascular disease and/or diabetes, thereafter.

Implications and public health

The findings of this review suggest that circulating IGF-I and IGFBP-3 may be of potential importance for cancer risk assessment and prevention. The use of IGF-I and IGFBP-3 measurements as surrogate markers of response to prevention interventions is currently being piloted [104,105]. Taken together, cancers of the prostate, colorectal, breast, and lung account for over two million new cases in developed countries per annum [106]. As the evidence to date has typically been based on risk for the upper quartile of a population, the contribution of altered levels of IGFs to the burden of cancer may be considerable. As the measurement of serum total IGF-I is relatively easy to perform and inexpensive, there is

scope to draw parallels with the measurement of serum cholesterol and cardiovascular disease risk. A further analogy is that the IGF peptides exist as an expanded family within the circulation, and with the availability of reliable assays to measure free IGF-I [107], IGFBP-1/IGF-I binary complexes [108], and IGFBP-3 proteolytic activity [109], it may be possible to build up an 'IGF serum profile' for individuals that may enhance cancer risk assessment. Short of examples of expensive and labour intensive proteomic assessments [110], there are few examples of a promising 'blood test' for cancer risk assessment.

Conclusions

There is now considerable evidence from human and laboratory studies supporting the hypothesis that circulating levels of IGF-I and IGFBP-3 influence the development of common cancer, of which increased risk of pre-menopausal breast cancer is now established. It is becoming increasing important that the clinical breast oncologist understands the physiology of the IGF system and its potential role in cancer risk assessment and prevention.

Potential conflicts of interest

A.G.R. and S.M.S. have received hospitality from Diagnostic Systems Laboratories, and from several pharmaceutical companies that make human growth hormone. A.G.R. has received a lecture honorarium from Eli-Lilly. S.M.S. receives research funding from Pfizer, Novo Nordisk and Novartis.

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