

Insulin-like Growth Factors and Prostate Cancer

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There is considerable inter-individual variation in the circulating concentrations of insulin-like growth factor I (IGF-I) and the insulin-like growth factor binding proteins. Recent research, including three prospective population studies, has provided evidence that men with higher levels of IGF-I and/or lower levels of its major binding protein are at increased risk for prostate cancer. These epidemiologic results are biologically plausible given earlier laboratory data concerning influences of insulin-like growth factor physiology on the prostate gland. Further research is needed 1) to describe in more detail the relation between insulin-like growth factor related analytes and prostate cancer risk, 2) to clarify the biologic mechanisms underlying the epidemiologic observations, and 3) to examine implications for prostate cancer diagnosis, prevention, and treatment. This presentation summarizes both the background and recent progress in this field.

BACKGROUND

Insulin-like growth factor physiology

Peptide growth factors play key roles in regulating the proliferation, differentiation, and death of cells. Many peptide growth factors are described as "tissue growth factors", a term which indicates that their synthesis and action do not involve the circulation. This distinguishes them from classic hormones, which are delivered via the circulation from organs where they are synthesized to their target sites of action. While most tissue growth factors are detectable in the circulation, their levels have not been the subject of epidemiologic investigations, as there is little evidence that these levels have biologic significance. In contrast, circulating levels of IGF-I are physiologically regulated, appear to be related to tissue bioactivity of the peptide, and vary substantially between normal individuals. Thus, IGF-I has characteristics of both a classic hormone and a tissue growth factor, and is an interesting analyte for population studies (1-3). Figure 1 provides a simplified outline of IGF-I physiology at the

whole organism and target tissue levels.

The pathologic conditions of acromegaly and growth hormone deficiency are related to excess and deficient IGF-I, respectively, and the initial clinical relevance of insulin-like growth factor physiology related to these diseases. Acromegaly is a consequence of growth hormone secreting neoplasms, usually of the pituitary gland. As growth hormone upregulates IGF-I expression, acromegaly is associated with IGF-I excess. Obvious clinical evidence for a relation between tissue IGF-I action and circulating IGF-I levels is provided by the correlations between the manifestations of acromegaly and of growth hormone deficiency with IGF-I levels.

There is a broad normal range of circulating IGF-I levels between the pathologic extremes of acromegaly and growth hormone deficiency. Until recently, relatively little attention was given to the biologic significance of inter-individual variability within this normal range. Twin studies have demonstrated that about half of the inter-individual variability is attributable to genetic factors (which remain largely uncharacterized, but now are being elucidated) and about half to non-genetic factors, which include age, dietary influences, and others (4, 5). Most circulating IGF-I originates in the liver, but recent experimental studies have emphasized that local production of IGF-I within insulin-like growth factor responsive tissues is important physiologically (6). It has been proposed (1) that hepatic IGF-I production, circulating IGF-I levels, and local IGF-I production in insulin-like growth factor responsive tissues may vary in parallel. If this is the case, then circulating IGF-I levels may represent a surrogate for tissue IGF-I bioactivity.

Insulin-like growth factor II (IGF-II), insulin-like growth factor binding proteins, and insulin-like growth factor receptors must be considered in addition to IGF-I. Both IGF-I and IGF-II act as mitogens by activating the IGF-I receptor, which is present on most cell types. IGF-I signal transduction is beyond the scope of this review, but has been summarized elsewhere (7, 8). In general, insulin-like growth factor signaling favors cell survival and/or proliferation over apoptosis or growth arrest. IGF-II is present in the circulation at high concentrations and is also locally produced in tissues, but there is no evidence to suggest a relation between circulating levels and local production. Therefore, IGF-II may be regarded more as a "tissue growth factor", as defined above, than IGF-I. The IGF-II receptor is now regarded by most investigators as a "decoy" rather than a receptor in the classic sense. It binds IGF-II with high affinity, thereby reducing the IGF-II available for binding to the

Abbreviations: IGF-I, insulin-like growth factor I; IGF-II, insulin-like growth factor II; IGFBP-1, insulin-like growth factor binding protein 1; IGFBP-2, insulin-like growth factor binding protein 2; IGFBP-3, insulin-like growth factor binding protein 3.

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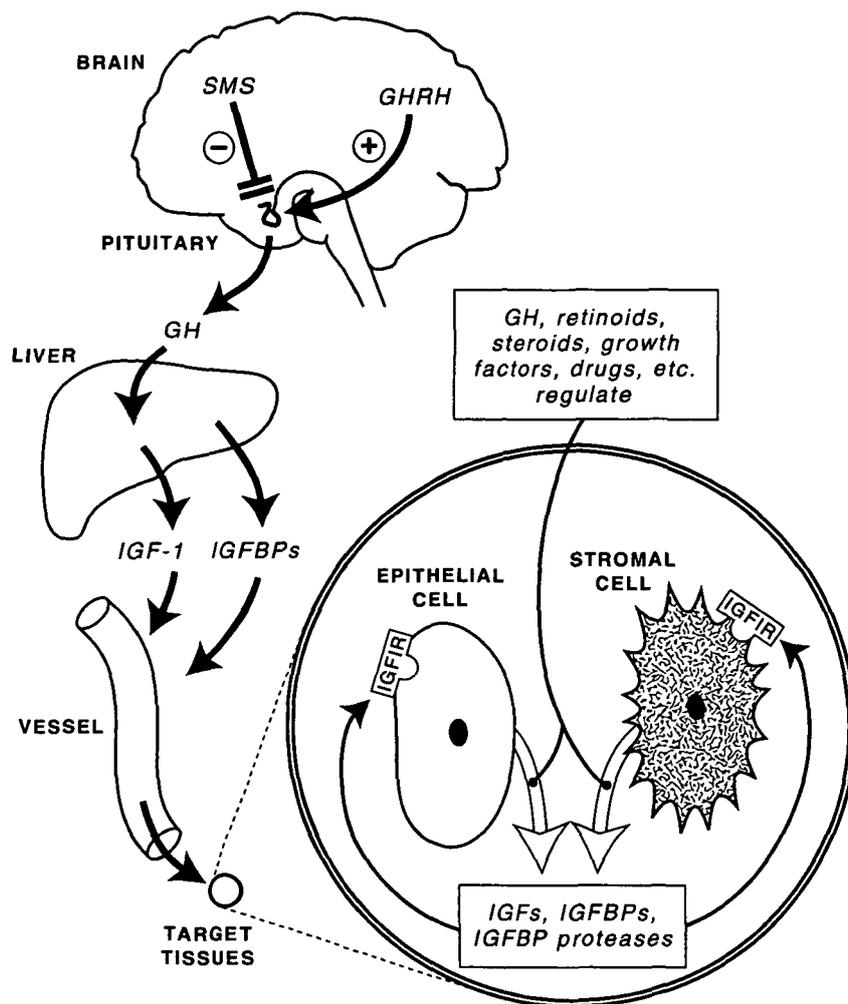


FIGURE 1. Simplified cartoon to outline insulin-like growth factor (IGF) physiology at the whole organism and tissue levels. GH, growth hormone; GHRH, growth hormone-releasing hormone; IGF-I, insulin-like growth factor I; IGFBP, insulin-like growth factor binding protein; IGFIIR, insulin-like growth factor I receptor; SMS, somatostatin.

IGF-I receptor. Overexpression of the IGF-II receptor tends to reduce, rather than increase, proliferation, raising the possibility of a tumor suppressor role for this molecule.

Less than 5 percent of circulating IGF-I is free; the bulk is complexed with circulating insulin-like growth factor binding proteins, of which at least six have been cloned (9). These proteins bind insulin-like growth factors with affinities comparable to insulin-like growth factor receptors. Most circulating insulin-like growth factors are complexed with insulin-like growth factor binding protein 3 (IGFBP-3) and an additional protein known as the acid-labile subunit. This complex cannot cross the capillary wall as easily as free insulin-like growth factors. Insulin-like growth factors in the circulation are in complex equilibria between free ligands, complexes with IGFBP-3, and lower molecular weight complexes. Interestingly, growth hormone, which is a key upregulator of IGF-I, also upregulates IGFBP-3 and acid-labile subunit expression—therefore, there is only a subtle increase in the IGF-I to IGFBP-3 ratio in acromegaly.

Importantly, the insulin-like growth factor binding proteins have functions beyond simple carrier molecules in the circulation, as evidenced by the fact that they are found in interstitial fluids. Here they act to modulate bioavailability of insulin-like growth factors, generally in a negative fashion. Insulin-like growth factor binding proteins are often expressed by insulin-like growth factor responsive cells and are subject to complex regulation. For example, cells that are growth-stimulated by estrogens and growth-inhibited by anti-estrogens decrease IGFBP-3 expression on estrogen exposure and increase IGFBP-3 expression on exposure to anti-estrogens (10). The apoptosis of the prostate gland associated with androgen deprivation also is associated with upregulation of insulin-like growth factor binding protein expression (11). This is one of several mechanisms by which growth-modulating actions of gonadal steroids involves “tuning” of insulin-like growth factor signaling. Other growth inhibitors whose action is correlated with induction of IGFBP-3 expression include transforming

growth factor β and retinoids (12) and vitamin D-related compounds (13, 14).

A further level of regulation involves insulin-like growth factor binding protein proteases, which cleave insulin-like growth factor binding proteins and increase bioavailable insulin-like growth factor concentrations. Prostate-specific antigen is a protease which cleaves IGFBP-3, thereby increasing insulin-like growth factor bioactivity in the cellular microenvironment (15). In the circulation, the presence of various protease inhibitors reduces the enzymatic activity of prostate-specific antigen: this is why most studies have not found a negative correlation between circulating IGFBP-3 and prostate-specific antigen levels.

Epidemiologists should recognize that we are currently in a period of rapid advances in insulin-like growth factor basic science. For example, recent laboratory work has provided evidence that certain insulin-like growth factor binding proteins (particularly IGFBP-3) may have direct growth-inhibitory actions unrelated to their insulin-like growth factor binding properties (16), and a new class of insulin-like growth factor binding protein-related proteins has been described (17). There is early evidence that certain polymorphisms may influence the circulating levels of insulin-like growth factors and insulin-like growth factor binding proteins. The first report concerned the gene encoding IGF-I itself (18), but its significance remains an active research topic (19). Further recent work provides evidence that both IGFBP-3 serum levels and gene expression are influenced by a polymorphism in the promoter region of the *IGFBP-3* gene (20), and that this polymorphism influences the ability of retinoids to induce IGFBP-3. If IGFBP-3 is indeed an important mediator of retinoid action as suggested by results in certain tissue culture systems (12), the polymorphism may define subpopulations more or less responsive to retinoids used as chemopreventative agents. Many issues remain to be elucidated, however, including, for example, the physiologic basis for and significance of unusual IGF-I to IGFBP-3 ratios seen in a minority of individuals in screened populations (21).

Insulin-like growth factors, the prostate, and prostate cancer

Early evidence for relevance of the insulin-like growth factor system to the prostate came from tissue culture studies that demonstrated *in vitro* responsiveness of prostate epithelial cells to insulin-like growth factors (22). More recently, *in vivo* experimental systems have provided further data indicating effects of insulin-like growth factor physiology on the prostate. Examples include demonstrations that IGF-I is required for prostate development (23), that systemic administration of IGF-I causes rat prostate growth (24), that overexpression of IGF-I in the prostate leads to transformation (25), that IGF-I deficiency is associated with reduced proliferation of prostate epithelial cells (2), and that prostate cancer progression in the transgenic adenocarcinoma of mouse prostate (TRAMP) model is associated with increased IGF-I expression (26). Interestingly, there is also *in vivo* evidence that treatments

and prevention strategies for prostate cancer impact insulin-like growth factor physiology. The reduction in prostate weight associated with finasteride administration (27), vitamin D analogue administration, (14) or castration (11) are all associated with upregulation of insulin-like growth factor binding protein expression, and suppression of prostate tumor growth by a growth hormone-releasing hormone antagonist is associated with suppression of IGF-II expression by neoplastic cells (28). Insulin-like growth factor-induced activation of the androgen receptor has been reported (29).

Insulin-like growth factor-related analytes in epidemiologic studies

Total circulating concentrations of IGF-I, IGF-II, and the binding proteins, insulin-like growth factor binding protein 1 (IGFBP-1), insulin-like growth factor binding protein 2 (IGFBP-2), and IGFBP-3, have been used in recent population studies. Newer assays include free IGF-I, free IGF-II, intact and fragmented IGFBP-3, and assays for additional insulin-like growth factor binding proteins and insulin-like growth factor binding protein-related proteins. Enzyme-linked immunosorbent assay (ELISA) methodology is most commonly used in epidemiologic studies, but radioimmunoassays have been in use longer and still are preferred by some laboratories.

The assay methodology for these and other insulin-like growth factor-related analytes is in evolution and remains challenging. Careful attention is needed to ensure sample quality and suitability. Uniform handling of samples is important. Optimally, whole blood samples should be kept cool and centrifuged within 2 hours of venipuncture. After centrifugation, serum or plasma should be frozen at -80°C or colder prior to assay. Different assay reagents may be designed specifically for serum or samples anticoagulated with ethylenediaminetetraacetic acid (EDTA) or heparin. Thawing should be done slowly at low temperatures.

Sample sets collected in the past for other purposes may or may not be suitable for assay and should be validated prior to undertaking large epidemiologic studies. One simple method to gain confidence in the technical suitability of samples is to ensure that both the expected negative correlation of age and IGF-I level and the expected positive correlation between IGF-I and IGFBP-3 levels are detectable. If these are not found, it is likely that a problem has occurred in at least some samples at venipuncture, handling of whole blood prior to centrifugation, freezing, thawing, or assaying, and the sample set should not be used to test new hypotheses. We recommend routine reporting of these control data, as well as the use of embedded blinded quality control samples, recombinant controls, and serum standards to detect assay drift. Using technically unsuitable sample sets is likely to yield falsely negative conclusions related to the hypothesis under study.

Absolute values obtained may vary between reagents provided by different manufacturers, different production lots of the same manufacturer, or assay laboratory, so appropriate controls are needed before attempting to pool data

obtained from different laboratories, or even data obtained from a single laboratory run at different times. Improved assay methodology and the more widespread use of international standards may alleviate some of these concerns in the future. Lack of precision in absolute values, provided that relative values are accurate, may not affect estimates of relative risk. However, it is recognized that to allow comparisons between different studies and to provide estimates of "normal levels" for different populations, standardization of methodologies to allow for accuracy in absolute values is desirable.

RECENT EPIDEMIOLOGIC DATA CONCERNING INSULIN-LIKE GROWTH FACTORS AND PROSTATE CANCER

Recent research carried out at several independent centers has shown a relation between circulating IGF-I concentration or the IGF-I/IGFBP-3 ratio and risk of prostate cancer (30–36). The first of three prospective studies was carried out using samples from the Physicians' Health Study (31). This investigation showed a relative risk of 4.3 when comparing the highest with the lowest quartiles of IGF-I. These data imply a strong relation of potential clinical significance; to put the result in context, it is instructive to recognize that in the same cohort, the relative risk for myocardial infarction was 2.51 when comparing the highest versus the lowest quartiles of cholesterol concentration (37, 38). Harman et al. (35) reported consistent findings from the prospective Baltimore Longitudinal Study on Aging. These investigators reported a relative risk for prostate cancer of 3.11 when comparing the highest versus lowest tertile of IGF-1 in a multivariate analysis. The third prospective study to investigate the relation between prostate cancer and IGF-1 level was carried out using the Northern Sweden Health and Disease Cohort and was reported by Stattin et al. (36). This study showed an odds ratio of 1.7 for prostate cancer when comparing highest versus lowest quartiles of IGF-1 level. While these three prospective studies were consistent in terms of their general conclusion, in that all showed a trend for increase in prostate cancer risk with increase in IGF-1 level in multivariate analysis, they did differ with respect to results concerning factors that modify or interact with IGF-1-related risk, making this a high priority area for future research. For example, the Physicians' Health Study and the Baltimore Longitudinal Study on Aging both observed a trend for an inverse relation between IGFBP-3 concentration and prostate cancer risk, while the Swedish study did not.

The observation that IGF-1 and IGFBP-3 were oppositely related to risk even though they are positively correlated with each other was unexpected and focused attention on the hypothesis that the ratio of these analytes might have significance. There are at least two biologic interpretations. First, it has been proposed that the ratio serves as a surrogate for free or bioavailable insulin-like growth factors. Alternatively, it is possible that the serum levels themselves are correlated with risk simply because they function as surrogates for the local expression of IGF-1 and IGFBP-3 within prostate tissue. According to this hypothesis, insulin-like growth factors

delivered through the circulation to the prostate may be of relatively minor importance, but individuals who have higher IGFBP-3 levels in the blood also have higher IGFBP-3 expression within the prostate, and this might be correlated with lower prostate cancer risk.

It is clear that we are at an early stage in understanding the relations between insulin-like growth factor binding protein levels and risk. Technical factors may account for some of the discrepancies between studies in this area. It is noteworthy that the three prospective studies used different antibodies to measure IGFBP-3 levels, and that the assays may vary in their ability to detect IGFBP-3 fragments as compared with intact IGFBP-3. One study (39) reported that IGFBP-1 was positively associated with prostate cancer risk. The authors speculated that high binding protein-1 levels may influence the kinetics of insulin-like growth factor movements between the vascular and extravascular compartments.

Case-control studies with results consistent with the prospective studies above include those of Wolk et al. (Sweden) (32), Chokkalingam et al. (China) (33), Mantzoros et al. (Greece) (34), and Djavan et al. (Austria) (30). An overview of a subset of the data now available (40) concluded that the evidence favored a relation between IGF-I and risk. However, several recent reports have failed to show an association. These include those of Finne et al. (41), Cutting et al. (42), Shariat et al. (43), and Kurek et al. (44). A formal meta-analysis of all these studies would be hazardous as they differ in important ways, including assay methodology, statistical methodology, selection of the study population, the definition of "case", and the nature of the control groups. For example, both cases and controls in the study of Finne et al. (41) had elevated prostate-specific antigen levels, indicating a study population that differed from the three prospective studies. It is conceivable that prostate cancer risk may vary with IGF-1 level for subjects with a normal prostate-specific antigen level, but not show a consistent relation with risk among men with elevated prostate-specific antigen levels.

Some case-control studies compared prostate-specific antigen levels to IGF-1 levels as predictors of positive prostate biopsies. It is not surprising that prostate-specific antigen levels are much more accurate predictors of positive biopsies than IGF-1 levels, because prostate-specific antigen is clearly a tumor marker while there is no clinical evidence that IGF-I is. However, this does not provide evidence against the hypothesis that high IGF-I levels represent a risk factor for prostate cancer.

BIOLOGIC INTERPRETATION OF RECENT EPIDEMIOLOGIC DATA

It is biologically plausible that inter-individual variation in insulin-like growth factor physiology, as reflected by inter-individual differences in circulating levels of IGF-related analytes, is related to inter-individual variation in prostate cancer risk. Figure 2 provides simplified cartoons illustrating insulin-like growth factor actions that may contribute to carcinogenesis and neoplastic progression. Men with higher IGF-I levels and/or lower IGFBP-3 levels may

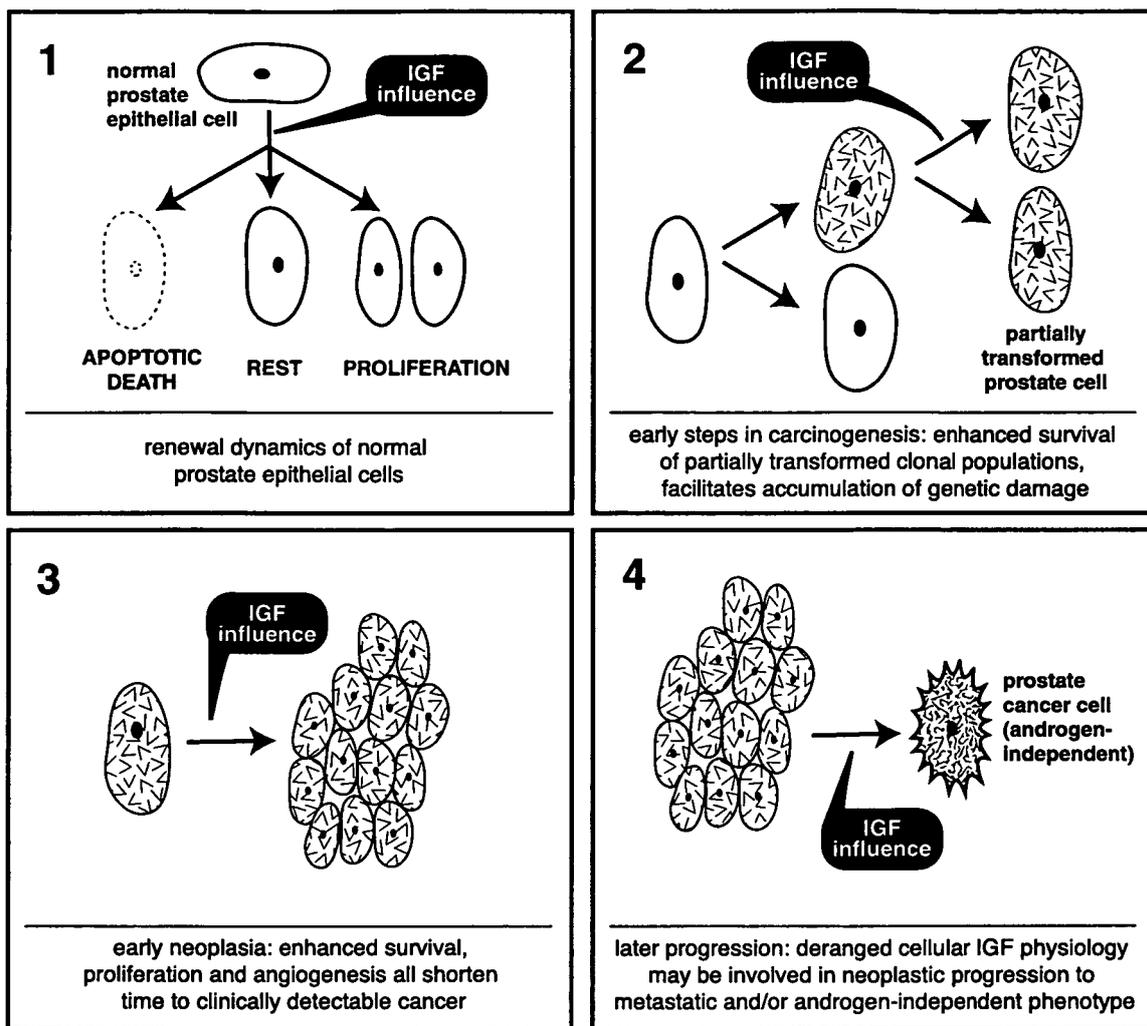


FIGURE 2. Simplified cartoons to illustrate possible insulin-like growth factor (IGF) actions that may relate to the relation between IGF levels and prostate cancer risk.

have subtly higher tissue insulin-like growth factor bioactivity. Over decades, this might result in billions of extra divisions and more opportunities for genetic “accidents”. In addition, the probability of survival of cells with single genetic “hits” might be somewhat higher in those men with higher IGF-I levels; this would increase the pool of cells available for second (or subsequent) “hits” and full transformation. Alternatively, the main influence of host insulin-like growth factor physiology may be after transformation. In this scenario, insulin-like growth factor physiology has little influence on early events in carcinogenesis, but, rather, affects the probability of a neoplasm remaining clinically insignificant versus progressing. Interestingly, these mechanistic speculations predict distinct results of epidemiologic research. For example, if the major influence of insulin-like growth factor physiology involves the probability of progression of early cancers, then it is likely that studies which define “case” as clinically detected prostate cancer will show stronger associa-

tions than studies that define “case” in terms of minimal cancers detected on the basis of minimal elevations of prostate-specific antigen.

An important *in vivo* prostate cancer model (26) suggests the possibility that circulating IGF-I may represent a tumor marker (i.e., originate from neoplastic cells) rather than a risk factor. On the other hand, the finding of an association between risk and IGF-I levels in a prospective study where blood sampling preceded diagnosis by many years would seem to be more compatible with a true “risk factor” than a “tumor marker” interpretation. This remains an active research issue. It must be emphasized that the distinction between “risk factor” and “disease marker” is often blurred. In contrast to hypercholesterolemia, which clearly is a risk factor for myocardial infarction and not a marker of this condition, minimal elevations of prostate-specific antigen have been described as a “risk factor” for a future prostate cancer diagnosis, but in this case the “risk factor” may simply reflect early diagnosis.

POTENTIAL CLINICAL RELEVANCE AND CURRENT RESEARCH ISSUES

Currently available data suggest that insulin-like growth factor-related risk influences probability of prostate cancer in a significant subset of the population. The disease burden attributable to common factors associated with moderate risk often exceeds that associated with rare factors associated with very high risk, even though the latter are obviously easier to identify. Additional rigorous studies to better describe the prostate cancer-insulin-like growth factor relation are necessary, given the potential importance of the results to date. Such work may shed light on the discrepancies between reported studies, and address the important issue of interactions between insulin-like growth factor-related risk and other risk factors.

One area of research that has been stimulated by the recent results involves the description of genetic and non-genetic factors that determine IGF-I and IGFBP-3 levels, and their ratio. The fact that the ratio, as well as the absolute values, of these analytes is physiologically regulated and may have medical significance is shown by the fact that the pubertal growth spurt is accompanied not only by an increase in IGF-I and IGFBP-3 levels (which is well recognized), but also by an increase in the ratio (45). Furthermore, evidence (21) that a small proportion of the population fails to show the expected correlation of IGF-I and IGFBP-3 requires follow-up. Those individuals with higher IGF-I/IGFBP-3 ratios may have subtle variations in regulation of gene expression that predispose to prostate cancer.

It is well known that starvation (which is known to reduce carcinogenesis in experimental systems) lowers IGF-I levels (5). Recent clinical studies provide evidence that dietary factors that influence prostate cancer risk also influence insulin-like growth factor physiology. High total caloric intake was shown to be associated with increased IGF-I levels (46), while the diet of vegans was associated with lower levels (47). There is also early evidence that individuals with higher circulating retinol level have higher circulating IGFBP-3 levels (20), and that lycopene, previously found to be negatively related to prostate cancer risk (48), interferes with insulin-like growth factor signal transduction (49). Silibinin, which has antiproliferative actions on prostate cells, also induces IGFBP-3 expression (50). It also is intriguing to speculate that the physiologic basis for the observation that height and body mass index are associated with prostate cancer risk (51) may involve insulin-like growth factor physiology. Furthermore, two studies (52, 53) have shown that ethnic groups with lower prostate cancer risk tend to have higher levels of IGFBP-3. While this does not demonstrate causality, it is an observation that requires follow-up.

With respect to genetic determinants, there are dozens of candidate genes that logically might be expected to influence IGF-I and/or IGFBP-3 levels. A recent report (20) has demonstrated a significant relation between genotype at a polymorphic site in the *IGFBP-3* promoter region and circulating IGFBP-3 level, and ongoing research is examining other candidate genes and also using genome-wide approaches to identify additional genetic determinants.

The ultimate clinical utility of a novel risk factor concerns applications related to cancer prevention. It is of interest that several approaches to prostate cancer prevention already under study, including the use of vitamin D-related compounds (13, 14), finasteride (27), and other androgen-targeting approaches (11, 54, 55), are known to upregulate insulin-like growth factor binding protein expression. It remains unclear to what extent, if any, the beneficial effects of these agents are attributable to their impact on insulin-like growth factor physiology, and this is the subject of ongoing investigations.

It is possible that serum markers or genetic markers related to insulin-like growth factor physiology may have utility in defining subsets of men more or less likely to benefit from particular pharmacologic or lifestyle prevention strategies. A prevention strategy that has only borderline efficacy when applied to the population as a whole may be found to have important risk reduction benefits in biologically defined subsets of men. It also is possible that serum markers related to insulin-like growth factor physiology may be useful as intermediate end points for chemoprevention interventions. It has been proposed (1, 2) that agents such as growth hormone antagonists (56), somatostatin analogues (57), or growth hormone-releasing hormone antagonists (28) may represent pharmacologic tools to lower IGF-I levels from the high-normal to low-normal range for men at increased risk. While it is clearly premature to propose large scale prevention trials with these or similar agents, the possibility of phase II pilot studies in very high risk men, such as those with prostate intraepithelial neoplasia, remains open.

Wolk et al. (58) have proposed that insulin-like growth factor-related analytes may find application in improving the sensitivity of prostate-specific antigen screening programs. This direction of research is at an early stage, but the possibilities that IGF-I level might be used to define men for whom prostate-specific antigen screening is particularly worthwhile, or to improve the predictive value of elevated prostate-specific antigen measurements, deserves study. Djavan et al. (30) have explored the use of IGF-I to prostate-specific antigen ratios for prostate cancer detection.

The question of implications of recent results concerning insulin-like growth factor-related prostate cancer risk and the use of growth hormone replacement therapy has been raised (59, 60). There is no evidence to date that prostate cancer risk is increased among men who receive growth hormone, but this cannot be regarded as completely reassuring. We would hypothesize that risk of such therapy, if it exists at all, might only be manifest after 10 or more years exposure, and long-term follow-up data are sparse. We would predict that the fact that any risk associated with growth hormone therapy would be mitigated by the fact that growth hormone stimulates both insulin-like growth factor and IGFBP-3 production. However, more quantitative data are needed to document the relative effects of growth hormone on these two proteins and to rule out the possibility that genetic polymorphisms define subtle differences between individuals in the impact of growth hormone therapy on the IGF-I/IGFBP-3 ratio. The absence of obvious excess of prostate cancer among acromegalics is also reassuring to a certain degree, but again caveats exist, including

issues of competing causes of mortality and the lack of data comparing IGF-I/IGFBP-3 ratios in treated or untreated acromegalics, normal men, and normal or growth hormone-deficient men receiving growth hormone therapy. At present, it would seem prudent to treat growth hormone deficiency with a goal of achieving mean IGF-I levels corresponding to the mean levels of age-specific controls rather than attempting to maximize IGF-I levels, particularly if treatment is planned for many decades.

Many investigators believe that carcinogenesis in the prostate gland is usually a process that proceeds over many decades, beginning at puberty. Height at puberty is related to IGF-I level (45). The secular trend towards increasing height (61–63) observed in certain countries may provide a clue that age-specific circulating IGF-I levels have been rising in certain human populations over the last century, perhaps in relation to changes in lifestyle and dietary factors such as total energy intake. It is conceivable that this may relate to some extent to the rise in prostate cancer incidence seen in recent decades. In the absence of appropriate serum archives, this is not a testable hypothesis, but it is one that is consistent with the recent prospective studies (31, 35, 36) that provide evidence for a relation between IGF-I level and prostate cancer risk.

The convergence over the past 2 years of epidemiologic and laboratory evidence linking insulin-like growth factor physiology to cancer risk in general, and to prostate carcinogenesis in particular, has generated considerable interest internationally (3, 64–67). It remains to be seen if this line of investigation will lead to clinical applications regarding prostate cancer diagnosis, treatment, or prevention, but there is no doubt that it represents an active field of research.

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