

IGF-I, insulin and prostate cancer

IGF-I, insulina e câncer de próstata

Giovanna A. Balarini Lima¹, Lívia L. Corrêa¹, Rafael Gabrich²,
Luiz Carlos D. de Miranda², Mônica R. Gadelha^{1,3}

ABSTRACT

Prostate cancer is the second most frequent malignancy diagnosed in adult men. Androgens are considered the primary growth factors for prostate normal and cancer cells. However, other non-androgenic growth factors are involved in the growth regulation of prostate cancer cells. The association between IGF-I and prostate cancer risk is well established. However, there is no evidence that the measurement of IGF-I enhances the specificity of prostate cancer detection beyond that achievable by serum prostate-specific antigen (PSA) levels. Until now, there is no consensus on the possible association between IGFBP-3 and prostate cancer risk. Although not well established, it seems that high insulin levels are particularly associated with risk of aggressive prostatic tumours. This review describes the physiopathological basis, epidemiological evidence, and animal models that support the association of the IGFs family and insulin with prostate cancer. It also describes the potential therapies targeting these growth factors that, in the future, can be used to treat patients with prostate cancer. *Arq Bras Endocrinol Metab.* 2009;53(8):969-75

Keywords

Insulin; IGF-I; prostate; cancer

RESUMO

O câncer de próstata é a segunda neoplasia mais frequentemente diagnosticada em homens adultos. Os androgênios são considerados fatores de crescimento primários para células prostáticas normais e malignas. Entretanto, outros fatores de crescimento não androgênicos estão envolvidos na regulação do crescimento das células prostáticas malignas. Associação entre IGF-I e risco de câncer de próstata é bem estabelecida. No entanto, não há evidência de que a dosagem do IGF-I melhore a especificidade na detecção do câncer de próstata, além daquela alcançada pelos níveis de antígeno prostático específico (PSA). Até hoje, não há consenso sobre a possível associação entre IGFBP-3 e risco de câncer de próstata. Apesar de não estar estabelecido, altos níveis de insulina parecem particularmente associados ao risco de tumores prostáticos agressivos. Esta revisão descreveu base fisiopatológica, evidências epidemiológicas e modelos animais que apoiam a associação da família das IGFs e insulina com câncer de próstata. Também foram descritas terapias potenciais que têm como alvo esses fatores de crescimento, os quais, no futuro, poderão ser usados para tratar pacientes com câncer de próstata. *Arq Bras Endocrinol Metab.* 2009;53(8):969-75

Descritores

Insulina; IGF-I; próstata; câncer

INTRODUCTION

Prostate cancer is the second most frequent malignancy diagnosed in adult men and the second cause of cancer death among Brazilian men (1). Androgens are considered the primary growth factors for prostate epithelial cells (2). However, other non-androgenic growth factors are involved in the growth regulation of

prostate cancer cells (2,3). Since the 1990's, the insulin-like growth factors (IGFs) family and insulin have been associated to different cancer types including prostate (4), colon (5-7), lung (8,9) and premenopausal breast cancers (10,11). Nonetheless, it was only in the last decade that there was a resurgence of interest in this issue. This review described the physiopathological basis,

¹ Serviço de Endocrinologia, Hospital Universitário Clementino Fraga Filho (HUCFF), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brasil
² Serviço de Urologia, HUCFF, UFRJ, Rio de Janeiro, RJ, Brasil
³ Serviço de Endocrinologia, Instituto Estadual de Diabetes e Endocrinologia Luiz Capriglione (IEDE), Rio de Janeiro, RJ, Brasil

Correspondence to:

Giovanna A. Balarini Lima
HUCFF, UFRJ
Rua Professor Rodolpho Paulo Rocco, 255, 9E23 – Cidade Universitária – Ilha do Fundão 21941-913 – Rio de Janeiro, RJ, Brasil
gibalarini@gmail.com

Received on Oct/13/2009

Accepted on Nov/8/2009

epidemiological evidence and animal models that support the association of the IGFs family and insulin with prostate cancer. We also described the new perspectives in anticancer therapies that, in the future, can be used to treat patients with prostate cancer.

PHYSIOPATHOLOGY OF IGFs FAMILY, INSULIN AND PROSTATE CANCER

The physiological development and growth of the prostate is primarily dependent on testosterone and dihydrotestosterone (2). However, the evidence that low androgen levels do not exclude prostate carcinoma suggests that other growth factors, such as insulin and the IGFs family, also have a role in the prostate carcinogenesis (12).

The effects of growth hormone (GH) are mediated primarily through the hepatic production of IGF-I. However, GH also has direct effects *in vivo* that are independent of IGF-I, many of which are exerted through local production of IGFs rather than under the influence of a factor in the circulation (13). Considering the prostate gland, the effects of the GH-IGF-I axis are exerted via: (a) direct action of GH; (b) hepatic IGF-I; and (c) IGF-I produced locally on the prostate tissue, through autocrine-paracrine action, possibly mediated by increase in the free IGF-I levels due to the action of prostate-specific antigen (PSA) and other proteases.

IGF-I is a potent mitogen for normal and cancerous cells (14) and exerts the mitogenic action by increasing DNA synthesis and by stimulating the cell cycle progression (15). In addition, IGF-I also inhibits apoptosis (16). Both IGF-I and, to a less extent, IGF-II have direct mitogenic and anti-apoptotic effects on normal and transformed prostate epithelial cells and have been implicated in the pathogenesis of prostate cancer (17-19).

The actions of IGF-I on cell proliferation and apoptosis are mediated via a specific cell-membrane receptor, IGF-I receptor (IGF-IR). Binding of IGF-I to IGF-IR activates the receptor's tyrosine kinase activity, which triggers a cascade of reactions among a number of molecules involved in the signal transduction pathway. Two distinct main signal transduction pathways have been identified. One pathway activates Ras protein, Raf protein and mitogen-activated protein kinase (MAPK). The other pathway involves activation of phosphatidylinositol 3-kinase (PI3K), AKT (or protein kinase B), mTOR (mammalian target of rapamycin) and S6 kinase (S6K) (20,21) (Figure 1).

The interaction between IGF-I and IGF-IR is regulated by the IGF-binding proteins (IGFBPs), so that under circumstances in which IGFBP levels are low, IGF mitogenic activity would be expected to be high (22). Of the circulating binding proteins, IGFBP-3 is the most abundant one (23). At the tissue level, IGFBP-3 serves an IGF carrier function, prolonging the half-life of the IGFs and regulating their availability to the cell surface receptors (24). In addition to its role as an IGF-I modulator, IGFBP-3 also has IGF-independent antiproliferative actions, such as inhibition of cell growth and stimulation of apoptosis (25,26). Many proteases that are present in prostate cancer microenvironment, including PSA, human kallikrein 2, trypsin and cathepsin D, can digest IGFBPs and release free IGF-I (27,28). The production of proteases by a cancer might therefore increase IGF-IR signaling.

Structurally, IGF-IR resembles the insulin receptor, and there is more than 50% homology between them (29). Because of this homology, insulin and IGF-I are able to cross-bind to each other's receptor or to the hybrid receptors (formed by an insulin half receptor and an IGF-I half receptor), albeit with much weaker binding affinity than that for the preferred ligand (30). Therefore, besides the classical metabolic actions of insulin, it also exerts proliferative and anti-apoptotic effects. The insulin signaling pathways are the same as the IGF-I's (Figure 1). The demonstration that both IR and IGF-IR are commonly expressed in human prostate cancer specimens (19) implicates insulin and IGF-I signaling in the initiation/progression of prostate cancer. In addition, the demonstration that the GHR

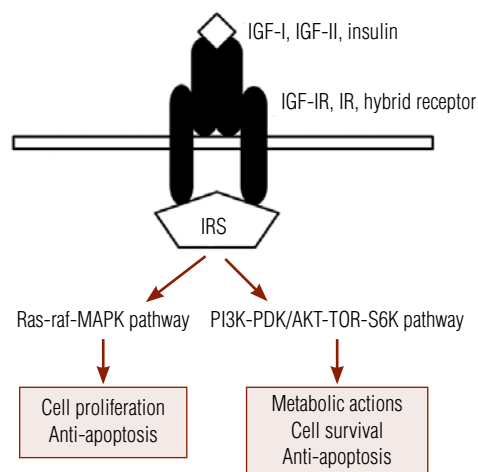


Figure 1. IGF-I and insulin receptor activation and downstream signaling.

IRS: insulin-receptor substrate; MAPK: mitogen-activated protein-kinase; PI3K: phosphatidylinositol 3-kinase; PDK: phosphoinositide-dependent protein kinase; TOR: target of rapamycin; S6K: S6 kinase.

is also expressed in prostate carcinoma tissues and that its mRNA levels are higher in carcinoma tissues than in benign prostate hyperplasia suggests that GH may play an important role in human prostate cancer (31).

The IGFs family also seems to be important in androgen-independent progression of prostate cancer. Activation of alternative autocrine, paracrine, or endocrine stimulatory pathways after androgen withdrawal initiate intracellular signal transduction pathways that can replace androgens for growth and survival of prostate tumor cells, either by bypassing the androgen receptor (AR) all together or by activating the AR. IGF-I, MAPK and AKT promotes non-ligand activation of AR, contributing to proliferation in an androgen depleted environment (32).

IGFS FAMILY AND PROSTATE CANCER: EPIDEMIOLOGICAL EVIDENCE

Retrospective and prospective epidemiological studies conducted in distinct populations have demonstrated that elevated serum IGF-I level is associated with an increased risk of prostate cancer. In 1997, a small Greek case-control study (n = 52) reported a multivariate relative risk (RR) of prostate cancer of 1.91 per 60 ng/mL increase in IGF-I level (95% confidence interval, CI: 1.00-3.73) (33). A larger case-control study (n = 210) from Sweden reported a similar positive association between IGF-I level and prostate cancer risk (34). A RR of 1.51 per 100 ng/mL increase in IGF-I level (95%CI: 1.00-2.26) was observed. In this study, the authors also examined IGFBP-3 and prostate cancer risk, but no significant association was observed.

In the Physicians' Health Study, a prospective epidemiological study, the associations between IGF-I and

IGFBP-3 levels and subsequent prostate cancer risk among 152 patients and 152 age-matched controls were investigated (17). A RR of 4.32 (95%CI: 1.76-10.6), if comparing men in the highest and lowest quartiles of IGF-I, when controlling for IGFBP3, was found. The corresponding RR for IGFBP3 was 0.41 (95%CI: 0.17-1.03). There was a significant linear trend between IGF-I and prostate cancer risk (RR: 2.1 per 100 ng/mL increase in IGF-I level; 95%CI: 1.3-3.2). No substantial change in this association was observed when adjusting for quartiles of weight, height, body mass index (BMI), plasma lycopene, and plasma hormone levels (estradiol, testosterone, dihydrotestosterone, sex hormone binding globulin (SHBG) and androstenediol glucuronide).

To date, five meta-analyses evaluating the association between IGF-I level, IGFBP-3 level and prostate cancer were published (Table 1). The first one (35) analyzed 14 case-control studies, and the combined data showed that circulating levels of IGF-I were significantly higher in prostate cancer patients. The odds ratio (OR) for prostate cancer was 1.47 (95%CI: 1.23-1.77) among men with high IGF-I compared to those with low IGF-I. A meta-analysis of nine prospective studies, that included 1,512 men with prostate cancer, found a similar risk (OR: 1.31; 95%CI: 1.03-1.71) (36). These findings were less significant than that reported by another meta-analysis that estimated a summary OR of 1.83 (95%CI: 1.03-3.26) for the association of the uppermost categories of serum IGF-I compared to the lowermost (6).

Recently, a collaborative reanalyzes of individual data from 12 prospective studies (n = 3,700 prostate cancer cases and 5,200 control participants) on the relationships between circulating levels of IGFs and sub-

Table 1. Meta-analyses evaluating IGF-I and IGFBP-3 levels (comparison of highest and lowest quantiles) and prostate cancer risk

Reference	IGF-I			IGFBP-3		
	Studies (n)	Cases (n)	OR (95%CI)	Studies (n)	Cases (n)	OR (95%CI)
Shi and cols. (35)	14	1,460	1.47 (1.27-1.71)	14	1,460	1.26 (1.03-1.54)
Renehan and cols. (6)	6	904	1.49 (1.14-1.95)	6	904	0.88 (0.61-1.28)
Morris and cols. (36)	9	1,512	1.31 (1.03-1.71)	9	1,512	1.05 (0.82-1.35)
Roddam and cols. (37)	12	3,671	1.38 (1.19-1.60)	12	3,600	1.23 (1.06-1.43)
Rowlands and cols. (4)	42	7,481	1.21 (1.07-1.36)	29	6,541	0.88 (0.79-0.98)

OR: odds ratio; 95%CI: 95% confidence interval.

sequent prostate cancer risk was conducted. A 38% increased odds of prostate cancer risk, comparing highest *versus* lowest quintiles of IGF-I (OR: 1.38; 95%CI: 1.19-1.60), was observed (37).

The largest systematic review of studies reporting on the association of IGF-I with the risk of prostate cancer was recently published (4). Unlike previous meta-analyses, this one included both retrospective and prospective studies (n = 42 studies) and demonstrated that the published literature is consistent with an average 21% increase risk of prostate cancer per standard deviation increase in IGF-I (OR: 1.21; 95%CI: 1.07-1.36). They also showed a stronger association of IGF-I with more aggressive (OR: 1.21; 95%CI: 0.97-1.51) and advanced (OR: 1.41; 95%CI: 1.07-1.85) cancers, compared to nonaggressive (OR: 1.05; 95%CI: 0.99-1.12) and localized (OR: 1.10; 95%CI: 0.98-1.11) ones.

Differently from IGF-I, the association between IGFBP-3 and prostate cancer risk is not a consensus. Considering the five meta-analyses previously mentioned, two of them unexpectedly suggested that IGFBP-3 is positively associated with prostate cancer risk (35,37). The probable inverse association between IGFBP-3 and prostate cancer risk was only seen in retrospective, but not prospective studies, so that, when analyzed together, the overall data suggest no evidence for an association of prostate cancer with IGFBP-3 (4). Also, there is little evidence for a role of IGF-II, IGFBP-1 or IGFBP-2 in prostate cancer risk (4).

Although there is association between higher levels of IGF-I and prostate cancer risk (4,6,35-37), the addition of IGF-I measurement to the PSA level or free/total PSA index does not seem to enhance the specificity of prostate cancer detection in clinical practice (4,36). Also, IGF-I levels are not a useful marker of prostate cancer in men with elevated PSA levels (38,39).

The association of acromegaly – a disease characterized by high GH and IGF-I levels – and prostate cancer is described elsewhere in this issue (refer to Corrêa and cols.).

INSULIN AND PROSTATE CANCER: EPIDEMIOLOGICAL EVIDENCE

Prospective cohort studies showed either no association or prostate cancer risk reduction with elevated C-peptide or insulin levels (40,41). However, one study observed a higher risk of prostate cancer mortality for men with C-peptide levels in the highest *versus* the lowest quartile (RR: 2.38; 95%CI: 1.31-4.30) (42).

Type 2 *diabetes mellitus* (T2DM), characterized by both hyperinsulinemia and hyperglycemia, has been related to cancer development in many epidemiological studies. Diabetic patients experience a higher risk of developing colorectal (7), endometrial (43), pancreatic (44) and postmenopausal breast (45) cancer compared with non-diabetic individuals. On the contrary, a history of T2DM has been related to a reduction of prostate cancer risk (46). However, in a study that included more than 2,000 prostate cancer cases, the inverse association was confined to non-aggressive prostate tumours (47). This inverse association may be explained by the frequent occurrence of hypogonadism in patients with T2DM (48).

INSULIN, IGFS FAMILY AND PROSTATE CANCER: ANIMAL MODELS

The possibility of studying human prostatic cancer in *in vitro* and *in vivo* environment has allowed the development of important tools to study many aspects of the biology of this cancer.

Transgenic mice expressing human IGF-I in basal epithelial cells of prostate have been characterized (49). Transgene expression led to activation of the IGF-IR and spontaneous tumorigenesis in prostate epithelium. Typical and atypical hyperplasias, prostatic intraepithelial neoplasia and well differentiated adenocarcinomas appeared in these mice. They offer an animal model for prostate cancer that will allow study of the stepwise development of this disease and the mechanisms whereby IGF-I mediates this process.

The Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) model has been used to investigate the role of the GH-IGF-I axis on *in vivo* prostate carcinogenesis and neoplastic progression. This model was developed using a prostate-specific fragment of the rat probasin regulatory sequence to specifically target expression of the simian virus 40 (SV40) large tumor antigen-coding region in the prostate epithelium (50). The changes that occur during prostate carcinogenesis in these mice highly resemble human prostate transformation (50) and take place in the setting of normal serum androgen levels (51). Using the TRAMP model, a mice homozygous for *lit*, a mutation that inactivates the GHRH receptor (GHRH-R) and reduces circulating levels of GH and IGF-I, was generated (52). The *lit* mutation in the TRAMP model significantly reduced the percentage of the prostate gland showing neoplastic changes

and was also associated with improved survival. The results suggest that prostate carcinogenesis and progression may be influenced by germ line variation of genes encoding signaling molecules in the GH-IGF-I axis.

Also in the TRAMP model, it was found that the expression of IGF-I mRNA in the prostate is elevated in early cancer progression. Nonetheless, the expression of IGF mRNA is not increased in advanced and metastatic disease, suggesting that only organ-confined disease seems to be IGF-I dependent (53).

Using a murine model of prostate cancer generated with LNCaP human prostate cancer cells, it was demonstrated that tumors from mice on the high carbohydrate/high fat diet had higher levels of activated AKT and modestly higher insulin receptor levels than tumors from mice on the low carbohydrate/high fat diet. Serum from mice on the high carbohydrate/high fat diet was more mitogenic for LNCaP cells *in vitro* than serum from mice fed the low carbohydrate/high fat diet. A high diet in refined carbohydrates is associated with increased tumor growth and with activation of signaling pathways distal to the insulin receptor (54).

NEW PERSPECTIVES IN PROSTATE CANCER THERAPY TARGETING THE IGF FAMILY AND INSULIN

Converging data from laboratory, clinical and population studies suggest that the IGFs family is implicated in different cancers. These findings led to the development of novel anticancer therapies targeting this family.

In the last ten years, several drug development researches to design novel agents to target IGF signaling were proposed. Many drug candidates demonstrated antineoplastic activity in laboratory models (55-57). Since 2008, dozens of drug candidates are being evaluated in clinical trials. Strategies include a reduction of IGF-I levels or bioactivity, inhibition of IGF-IR function and inhibition of signaling pathways downstream to IGF-IR (Figure 2).

Reduction of IGF-I levels can be achieved with the use of GH releasing hormone antagonists, somatostatin analogs (e.g. octreotide, pasireotide) and GHR antagonist (pegvisomant). Octreotide, used together with complete androgen blockade, in patients with prostate carcinoma has beneficial results (58). *In vitro*, pegvisomant inhibits the proliferation of prostatic cancer cells (59).

Inhibition of IGF-IR function can be accomplished with the use of inhibitors of IGF-I binding

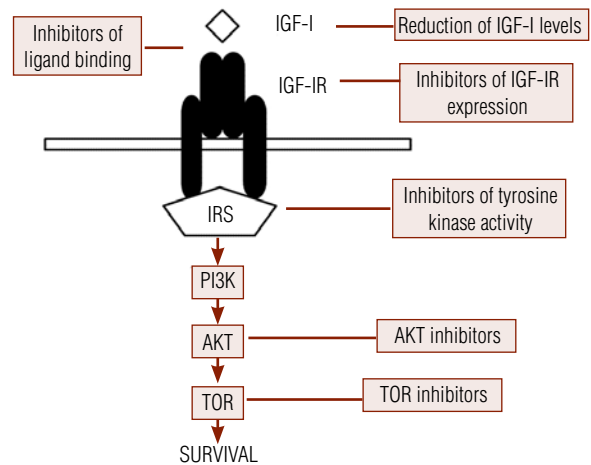


Figure 2. Therapeutic strategies targeting the IGF-I - IGF-IR signaling.

IRS: insulin-receptor substrate; PI3K: phosphatidylinositol 3-kinase; TOR: target of rapamycin.

(e.g. antireceptor antibodies), inhibitors of IGF-IR expression (e.g. antisense oligonucleotides, small interfering RNA) and inhibitors of tyrosine-kinase activity (60). Moreover, inhibition of IGF-IR downstream signaling pathways can be achieved with the use of AKT inhibitors and mTOR inhibitors (61).

Meanwhile, due to reports documenting insulin receptor on neoplasms and to evidence that higher serum insulin levels are associated with adverse cancer outcomes (42,62), the use of metformin in cancer patients is being investigated. Actually, population studies provided preliminary evidence that it might have antineoplastic or chemo preventing activity (63). Although often referred to as insulin-sensitizer, recent evidence suggests that the key mechanism of action of metformin is as an activator of the AMP-activated protein kinase (AMPK) pathway (64). By activating AMPK in the liver, it suppresses gluconeogenesis, leading to decreased hepatic glucose output and therefore to reduced blood glucose and insulin levels. In addition, metformin can increase AMPK activity in neoplastic cells, leading to downstream effects that include inhibition of mTOR signaling, protein synthesis and cell proliferation (Figure 3).

CONCLUSIONS

The association between IGF-I and prostate cancer risk is well established. In addition, a stronger association of IGF-I with more aggressive and advanced prostate cancers, when compared to nonaggressive and localized ones, is suggested. However, there is no evidence that the measurement of IGF-I enhances the specificity of prostate cancer detection beyond that achievable by the

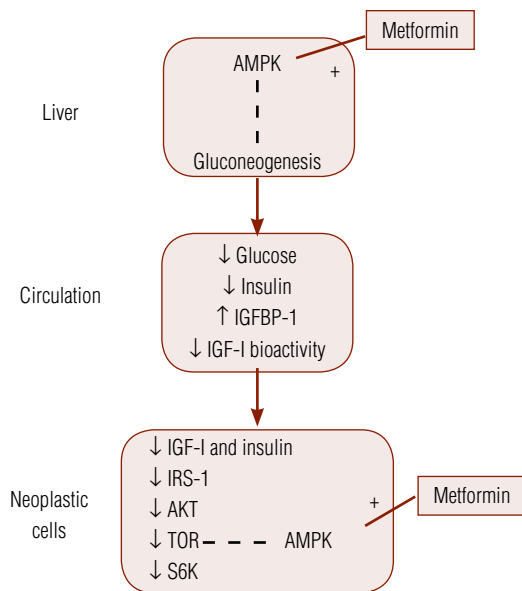


Figure 3. Metformin actions that may be important for prostate cancer treatment

AMPK: AMP-activated protein kinase; IRS: insulin-receptor substrate; TOR: target of rapamycin; S6K: S6 kinase. ----: inhibition; +: stimulation.

currently used serum PSA levels. Until now, there is no consensus on the possible association between IGFBP-3 and prostate cancer risk. Although not well established, it seems that high insulin levels are particularly associated with risk of aggressive prostatic tumours. The development of drugs targeting IGF family and insulin represents a new perspective in the prostate anticancer therapy.

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES

1. Instituto Nacional do Câncer (INCA). Ministério da Saúde, Brasil. Available from: <http://www.inca.gov.br>.
2. Cuhna GR, Donjacour AA, Cooke PS, Mee S, Bigsby RM, Higgins SJ, et al. The endocrinology and developmental biology of the prostate. *Endoc Rev.* 1987;8(3):338-62.
3. Wilson JD. The pathogenesis of benign prostatic hyperplasia. *Am J Med.* 1980;68(5):745-56.
4. Rowlands M, Gunnell D, Harris R, Vatten LJ, Holly JMP, Matin RM. Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. *Int J Cancer.* 2009;124(10):2416-29.
5. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, 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.* 1999;91(7):620-5.
6. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet.* 2004;363(9418):1346-53.
7. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst.* 2005;97(22):1679-87.
8. Yu H, Spitz MR, Mistry J, Gu J, Hong WK, Wu X. Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis. *J Natl Cancer Inst.* 1999;91(2):151-6.
9. Wakai K, Ito Y, Suzuki K, Tamakoshi A, Seki N, Ando M, Ozasa K, Watanabe Y, Kondo T, Nishino Y, Ohno Y; JACC Study Group. 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.* 2002;93:1279-86.
10. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet.* 1998;351(9113):1393-6.
11. Muti P, Quattrin T, Grant BJ, Krogh V, Micheli A, Schunemann HJ, et al. Fasting glucose is a risk factor for breast cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev.* 2002;11(11):1361-8.
12. Morgentaler A, Bruning CO, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. *JAMA.* 1996;276(23):1904-6.
13. Kaplan SA, Cohen P. The somatomedin hypothesis 2007: 50 years later. *J Clin Endocrinol Metab.* 2007;92(12):4529-35.
14. Macaulay VM. Insulin-like growth factors and cancer. *Br J Cancer.* 1992;65(3):311-20.
15. Qu BH, Karas M, Koval A, Le Roith D. Insulin receptor substrate-4 enhances insulin-like growth factor-I-induced cell proliferation. *J Biol Chem.* 1999;274(44):31179-84.
16. Párrizas M, Saltiel AR, Le Roith D. Insulin-like growth factor I inhibits apoptosis using the phosphatidylinositol 3' kinase and mitogen-activated protein kinase pathways. *J Biol Chem.* 1997;272(1):154-61.
17. Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, et al. Plasma insulin-like growth factor-1 and prostate cancer risk: a prospective study. *Science.* 1998;279(5350):563-6.
18. Pollak M. Insulin-like growth factors (IGFs) and prostate cancer. *Epidemiol Rev.* 2001;23(1):59-66.
19. Cox ME, Gleave ME, Zakikhani M, Bell RH, Piura E, Vickers E, et al. Insulin receptor expression by human prostate cancers. *Prostate.* 2009;69(1):33-40.
20. Le Roith D, Werner H, Beitner-Johnston D, Roberts CT Jr. Molecular and cellular aspects of the insulin-like growth factor-I receptor. *Endoc Rev.* 1995;16(2):143-63.
21. Le Roith D. Regulation of proliferation and apoptosis by the insulin-like growth factor I receptor. *Growth hormone & IGF-I Res.* 2000;10 Suppl:S12-3.
22. Pollak M. Insulin and insulin-like growth factor signaling in neoplasia. *Nat Rev Cancer.* 2008;8(12):915-28.
23. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev.* 1995;16(1):3-34.
24. Baxter RC, Butt AJ, Schendlich LJ, Martin JL. Antiproliferative and pro-apoptotic activities of insulin-like growth factor binding protein-3. *Growth hormone & IGF-I Res.* 2000;10 Suppl A:S10-1.
25. Butt AJ, Firth SM, Baxter RC. The IGF axis and programmed cell death. *Immunol Cell Biol.* 1999;77(3):256-62.
26. Hong J, Zhang G, Dong F, Rechler MM. Insulin-like growth factor (IGF)-binding protein-3 mutants that do not bind IGF-I or IGF-II stimulate apoptosis in human prostate cancer cells. *J Biol Chem.* 2002;277(12):10489-97.
27. Cohen P, Graves HCB, Peehl DM, Kamarei M, Giudice LC, Rosenfeld RG. Prostate-specific antigen (PSA) is an insulin-like growth factor binding protein-3 protease found in seminal plasma. *J Clin Endocrinol Metab.* 1992;75(4):1046-53.
28. Koistinen H, Paju A, Koistinen R, Finne P, Lövgren J, Wu P, et al. Prostate-specific antigen and other prostate-derived proteases cleave IGFBP-3, but prostate cancer is not associated with proteolytically cleaved circulating IGFBP-3. *Prostate.* 2002;50(2):112-8.
29. Mynarcik DC, Williams PF, Schaffer L, Yu GO, Whittaker J. Identification of common ligand binding determinants of the insulin and

- insulin-like growth factor 1 receptors. Insights into mechanisms of ligand binding. *J Biol Chem*. 1997;272(30):18650-5.
30. Werner H, Weinstein D, Bentov I. Similarities and differences between insulin and IGF-I: structures, receptors, and signaling pathways. *Arch Physiol Biochem*. 2008;114(1):17-22.
 31. Weiss-Messer E, Merom O, Adi A, Karry R, Bidosee M, Ber R, et al. Growth hormone (GH) receptors in prostate cancer: gene expression in human tissues and cell lines and characterization, GH signaling and androgen regulation in LNCaP cells. *Mol Cell Endocrinol*. 2004;220(1-2):109-23.
 32. So A, Gleave M, Hurtado-Col A, Nelson C. Mechanisms of the development of androgen independence in prostate cancer. *World J Urol*. 2005;23(Part 1):1-9.
 33. Mantzoros CS, Tzonou A, Signorello LB, Stampfer M, Trichopoulos D, Adami HO. Insulin-like growth factor 1 in relation to prostate cancer and benign prostatic hyperplasia. *Br J Cancer*. 1997;76(9):1115-8.
 34. Wolk A, Mantzoros CS, Andersson SO, Bergström H, Signorello LB, Lagiou P, et al. Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. *J Natl Cancer Inst*. 1998;90(12):911-5.
 35. Shi R, Berkel HJ, Yu H. Insulin-like growth factor-I and prostate cancer: a meta-analysis. *Br J Cancer*. 2001;85(7):991-6.
 36. Morris JK, George LM, Wu T, Wald NJ. Insulin-like growth factors and cancer: no role in screening. Evidence from the BUPA study and meta-analysis of prospective epidemiological studies. *Br J Cancer*. 2006;95(1):112-7.
 37. Roddam AW, Allen NE, Appleby P, Key TJ, Ferrucci L, Carter HB, et al. Insulin-like growth factors, their binding proteins and prostate cancer risk: analysis of individual patient data from 12 prospective studies. *Ann Intern Med*. 2008;149(7):461-71, W83-8.
 38. Finne P, Auvinen A, Koistinen H, Zhang W-M, Määttänen L, Rannikko S, et al. Insulin-like growth factor I is not a useful marker of prostate cancer in men with elevated levels of prostate-specific antigen. *J Clin Endocrinol Metab*. 2000;85(8):2744-7.
 39. Ismail AH, Pollak M, Behloul H, Tanguay S, Bégin LR, Aprikian AG. Insulin-like growth factor-1 and insulin-like growth factor binding protein-3 for prostate cancer detection in patients undergoing prostate biopsy. *J Urol*. 2002;168(6):2426-30.
 40. Chen C, Lewis SK, Voigt L, Fitzpatrick A, Plymate SR, Weiss NS. Prostate carcinoma incidence in relation to prediagnostic circulating levels of insulin-like growth factor I, insulin-like growth factor binding protein 3, and insulin. *Cancer*. 2005;103(1):76-84.
 41. Hubbard JS, Rohrmann S, Landis PK, Metter EJ, Muller DC, Andres R, et al. Association of prostate cancer risk with insulin, glucose, and anthropometry in the Baltimore longitudinal study of aging. *Urology*. 2004;63(2):253-8.
 42. Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol*. 2008;9(11):1039-47.
 43. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia*. 2007;50(7):1365-74.
 44. Huxley R, Ansary-Moghaddam A, Berrington de GA, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer*. 2005;92(11):2076-83.
 45. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer*. 2007;121(4):856-62.
 46. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2006;15(11):2056-62.
 47. Leitzmann MF, Ahn J, Albanes D, Hsing AW, Schatzkin A, Chang SC, et al. Diabetes mellitus and prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Causes Control*. 2008;19(10):1267-76.
 48. Dhinsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab*. 2004;89(11):5462-8.
 49. DiGiovanni J, Kiguchi K, Frijhoff A, Wilker E, Bol DK, Beltran L, et al. Deregulated expression of insulin-like growth factor 1 in prostate epithelium leads to neoplasia in transgenic mice. *Proc Natl Acad Sci USA*. 2000;97(7):3455-60.
 50. Greenberg NM, DeMayo F, Finegold MJ, Medina D, Tilley WD, Aspinale JO, et al. Prostate cancer in a transgenic mouse. *Proc Natl Acad Sci USA*. 1995;92(8):3439-43.
 51. Wang J, Eltoum IE, Lamartiniere CA. Genistein alters growth factor signaling in transgenic prostate model (TRAMP). *Mol Cell Endocrinol* 2004;219(1-2):171-80.
 52. Majeed N, Blouin MJ, Kaplan-Lefko PJ, Barry-Shaw J, Greenberg MN, Gaudreau P, et al. A germ line mutation that delays prostate cancer progression and prolongs survival in a murine prostate cancer model. *Oncogene*. 2005;24(29):4736-40.
 53. Foster BA, Kaplan PJ, Greenberg NM. Peptide growth factors and prostate cancer: new models, new opportunities. *Cancer Metastasis Rev*. 1998-1999;17(4):317-24.
 54. Venkateswaran V, Haddad AQ, Fleshner NE, Fan R, Sugar LM, Nam R, et al. Association of diet-induced hyperinsulinemia with accelerated growth of prostate cancer (LNCaP) xenografts. *J Natl Cancer Inst*. 2007;99(23):1793-800.
 55. Goya M, Miyamoto S, Nagai K, Ohki Y, Nakamura K, Shitara K, et al. Growth inhibition of human prostate cancer cells in human adult bone implanted into non obese diabetic/severe combined immunodeficient mice by a ligand-specific antibody to human insulin-like growth factors. *Cancer Res*. 2004;64(17):6252-8.
 56. Haluska P, Carboni JM, Loegering DA, Lee FY, Wittman M, Saulnier MG, et al. In vitro and in vivo antitumor effects of the dual insulin-like growth factor-I/insulin receptor inhibitor, BMS-554417. *Cancer Res*. 2006;66(1):362-71.
 57. Ji QS, Mulvihill MJ, Rosenfeld-Franklin M, Cooke A, Feng L, Mak G, et al. A novel, potent, and selective insulin-like growth factor-I receptor kinase inhibitor blocks insulin like growth factor-I receptor signaling in vitro and inhibits insulin-like growth factor-I receptor dependent tumor growth in vivo. *Mol Cancer Ther*. 2007;6(8):2158-67.
 58. Sciarra A, Panebianco V, Ciccariello M, Salciccia S, Gentilucci A, Lisi D, et al. Complete response to the combination therapy with androgen blockade and somatostatin analogue in a patient with advanced prostate cancer: magnetic resonance imaging with ¹H-spectroscopy. *Eur Urol*. 2008;53(3):652-5.
 59. Schally AV, Varga JL. Antagonistic analogs of growth hormone-releasing hormone: new potential antitumor agents. *Trends Endocrinol Metab*. 1999;10(10):383-91.
 60. Hewish M, Chau I, Cunningham D. Insulin-like growth factor 1 receptor targeted therapeutics: novel compounds and novel treatment strategies for cancer medicine. *Recent Pat Anticancer Drug Discov*. 2009;4(1):54-72.
 61. Engelman JA. Targeting PI3K signaling in cancer: opportunities, challenges and limitations. *Nat Rev Cancer*. 2009;9(8):550-62.
 62. Wolpin BM, Meyerhardt JA, Chan AT, Ng K, Chan JA, Wu K, et al. Insulin, the insulin-like growth factor axis, and mortality in patients with nonmetastatic colorectal cancer. *J Clin Oncol*. 2009;27(2):176-85.
 63. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. *BMJ*. 2005;330(7503):1304-5.
 64. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest*. 2001;108(8):1167-74.