Growth hormone and Insulin like growth factor -1 in relation to prostate cancer and benign prostatic hyperplasia

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(Accepted for publication: December 19, 2016)

Abstract:

The present study investigate the role of growth hormone (GH) in the pathophysiology of prostate and the role of insulin like growth factor I (IGF-I) as a risk factor in aged male patients with prostate cancer (PCa) and benign prostatic hyperplasia (BPH). For this purpose, 40 patients with PCa and BPH (54-85 yr.), and 10 control subjects (47-75 yr.) confirmed by digital rectal examination (DRE) and prostate specific antigen (PSA) levels, were enrolled in this study. Blood samples and biopsies were collected from cases while for the control, only blood sera were used. Gleason grading system was used to determine histological pattern of Hematoxylin and Eosin stained sections. Sera GH and IGF-I were measured for all the samples using (ELISA) technique. Biopsy results revealed that 10 cases were identified as PCa with different Gleason grades (3, 4, and 5) depending on five histological patterns, and 30 cases were identified as BPH. Compared with control values, GH level was significantly higher (P< 0.05) in PCa and BPH patients, with no significant differences between PCa and BPH groups (P> 0.05) concerning serum GH level. Statistical analysis also indicates that serum levels of IGF-I was higher and significantly (P< 0.05) associated with PCa compared with controls. Serum IGF-I also showed significant difference between control and BPH patients, and between BPH and PCa patients. The present study demonstrated that the association between serum IGF-I levels and PCa was highly significant in age 60 and declined with the age (p= 0.047), but in concern to the histological grade, IGF-I showed no significant differences (p=0.894) with the progression of disease. In conclusion it's appeared that, IGF-I play an important role in the etiology of PCa and BPH.

Keywords: *Prostate cancer, Benign prostatic hyperplasia, Growth hormone, Insulin like growth factor I*

Introduction:

In men over 50 years of age, prostate cancer (PCa) and benign prostatic hyperplasia (BPH) are among the most commonly diagnosed malignant and benign prostate proliferative disorders respectively (Carter and Coffey, 1990). In developed countries, PCa is the most frequently diagnosed cancer and the second most common cause of cancer death among men (Ramsay and Leung, 2009). The etiology of PCa is unknown but it has been suggested that growth factors abnormalities may be involved in initiation and progression of this disease (Kehinde et al., 2005). BPH is a common neoplasm of the prostate and causes considerable morbidity in aging men (N'Dow and Wilt, 2008).

Prostate specific antigen (PSA) testing is the most important biomarker for diagnosing and monitoring of PCa (Brett, 2011). In 2013, Muhammad and Waheed, evaluate the significance of serum PSA as a screening tool for the detected PCa and the role of percent free - to- total PSA ratio in the discriminating between BPH and PCa and their results indicated that combinational use of tPSA with other molecular forms of PSA especially proportion of FPSA provide higher diagnostic and accurate tool than the tPSA alone

The risk of developing cancer is determined by a combination of genetic factors and environmental effects, in particular diet and living lifestyle. There is increasing evidence that the growth hormone (GH)/insulin-like growth factor (IGF)-I axis might provide a major link between these factors and the development of cancers through its influence on the regulation of normal cell proliferation, differentiation and apoptosis (Jenkins and Bustin, 2004).

Growth hormone could exert its actions directly on the prostate, through specific receptors (Reiter *et al.*, 1992). However, GH could also act indirectly, with its effects mediated by systemic IGF-I produced in the liver under GH control (Daughaday and Rotwein, 1989).

The GH/IGF axis plays an important role in regulating prostate epithelial cell proliferation and apoptosis both *in vitro* and *in vivo* (Moschos and Mantzoros, 2002). The role of IGFs in cancer is supported by epidemiologic

studies, which have found that high levels of circulating IGF-I and low levels of IGF-binding protein-3 (IGFBP-3) are associated with increased risk of several common cancers, including those of prostate, breast, colorectum, and lung (Yu and Rohan, 2000).

One of the principal hormonal stimuli for IGF-I production is GH (Copeland *et al*., 1980). Most circulating IGF-I and IGFBP-3 originates from the liver, and the key stimulus for production of these polypeptides in the liver and in many other tissues is GH (Le Roith *et al*., 2001), and expression of the IGF-I gene is regulated primarily by GH. Levels of circulating IGF-I change substantially with age, they increase slowly from birth to puberty, surge at puberty, and decline with older age (Jones and Clemmons, 1995).

Dysregulation and/or overexpression of the IGF system have long been implicated in the etiology of both benign and malignant proliferative disorders (Samani *et al*., 2007). So the current study was designed to investigate: the effect of GH and IGF-I levels in men with PCa and BPH as well as in healthy men with no apparent prostatic disorders confirmed by PSA levels and Digital Rectal Examination (DRE).

MATERIALS AND METHODS

SAMPLES COLLECTION

The total number of patients and healthy individuals were 50. All cases were collected from both Tooimalek Private Hospital and Urology Department in the Sulaimani Teaching Hospital. The present study includes of the following groups:

1- Control group: This group consisted of 10 individuals (47-75 yr.) with normal DRE and PSA levels within the normal range (< 4 ng/ml). These patients were admitted to Shaheed Sayfadeen Consultative Hospital for non-prostatic diseases (colorectal and kidney diseases).

2- BPH group: This group included 30 individuals (54-82 yr.). These patients were available for the study with abnormal DRE and PSA levels above the normal range > 4 ng/ml, and lower urinary tract symptoms, in addition to the histological confirmation.

3- PCa group: This group included 10 individuals with prostatic carcinoma (60-85 yr.). PCa diagnosis depended on both high PSA levels, and histological confirmation which included the determination of the Gleason grade by four expert histopathologists. Five of the cancers were grade IV (poorly differentiated), two grade III (moderately differentiated, one was high grade transitional cell carcinoma and one was primary transitional cell carcinoma) (Gleason, 1990).

The study protocol included the collection of prostatic biopsies for histopathological diagnosis of the samples, and blood samples were taken for hormonal (GH and IGF-I) assay.

BLOOD COLLECTION

Before obtaining any biopsy, blood samples were with drawn from all patients prior to prostatectomy at the hospital but for controls, five ml of venous blood was drawn at the time of interview, transferred into non-anticoagulant tubes, and allowed to clot for 15-30 minutes at room temperature. After clotting, the samples were centrifuged at 2500-3000 rpm for 10 min. and the sera were stored in a deep freeze at -30 °C. Both GH, IGF-I concentrations were measured using commercially available ELISA kits (Wolk *et al.,* 1998).

BIOPSIES COLLECTION AND PRESERVATION

Total of 40 prostate biopsies (10 PCa and 30 BPH) were taken from the patients during prostatectomy or transurethral resection of the prostate (TURP). Biopsy samples were preserved in 10% formalin solution. Formalin-fixed paraffin wax embedded samples were cut at a thickness of 5 µm to prepare using hematoxyline (Harris) and eosin stained slides were prepared to determine histopathological diagnosis (Carson, 1997).

HORMONAL ASSAY

DETERMINATION OF SERUM GH AND IGF-I

Hormonal tests were performed using commercially available ELISA kits. Serum levels of GH and IGF-I was assessed using kits supplied by (Biochek HGH kit, Cat.No. BC-1033, Canada), and (Biosource IGF-I-ELISA kit, Cat.No. KAPB2010) respectively, and according to the instructions of the manufacturers the absorption of GH and IGF-1 were measured spectrophotometrically. For GH at 450 nm. The concentration of HGH is directly proportional to the color intensity of the test sample. While in case of IGF-1 the intensity of the yellow color is measured using a spectrophotometer with a 405 nm filter. Patient sample concentrations of GH and IGH-1 were read from a calibration curve (Chan *et al*., 1998).

STATISTICAL ANALYSIS:

Analysis of data was performed using SPSS software (version 15). Results are expressed as mean ± standard error (M ± SE): P values ≤ 0.05 were considered significant.

RESULTS

Histopathological diagnosis of the biopsies specimens

The histopathological diagnosis of BPH are characterized by stromal nodules consisted of fibromuscular cell proliferation and the glands are lined by columnar epithelium with the fibromuscular stroma condensed at the periphery of the nodules (Figure 1A and B).

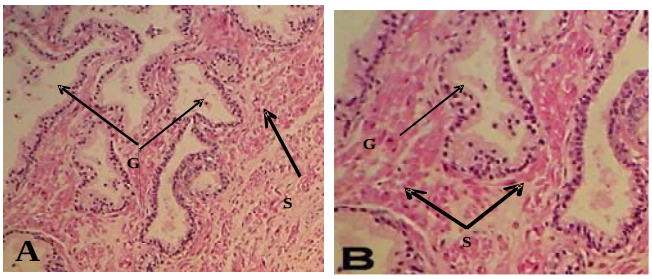

Figure (1): Section of BPH involves both glands and stroma . (A) (250X), (B) (400X). G =disrupted glands lined with columnar epithelium. S= stroma intervening glands. Fibromuscular stroma is condensed at the peripheral of the nodule.

Prostatic carcinoma

As mentioned above only 10 patients were diagnosed as PCa and they were of different histological grades as revealed by the histopathologists. Microscopic examination of carcinoma was characterized by angulated and distorted acini with an irregular arrangement and infiltrative growth pattern.

Acini vary size, shape, and spacing, and lack basal cell layer. The nuclei were enlarged; the presence of multiple nucleoli is strong evidence of malignancy.

Gleason Grading of Biopsies

Grading systems are different for each type of cancer, but in general, the lower grade mostly resembles the normal cell. The grade of a tumor helps determine the type of treatment. The results for the PCa biopsies were as follows:

1- Prostatic carcinoma grade 3 (3 cases):

Among the 10 carcinoma cases, 3 were of grade 3 depending on Gleason grading system. Grade 3 carcinomas as shown in Figure (2, A and B) exhibited rapid growth characterized by loss of cytocohesivity. The tumor cells often lie isolated and widely disseminated within the pre-existing prostatic stroma. There is barely a trace of a glandular pattern of growth. The larger the carcinoma, the more widely varied will be the mixture of histologic tumor patterns it exhibits. Pattern 3 adenocarcinoma glands are generally darker than well-differentiated patterns 1 and 2, which is due in part to cytoplasmic basophilia.

2- Prostatic carcinoma grade 4 (5 cases):

In grade 4 which was seen in 5 cases among the 10 cases, as shown in Figure (3) was recognized by the ragged edges or outlines of the invasive periphery compared to the smooth, pushing borders of pattern 3. The nuclei in pattern 4 may be deceptively bland. In these cases, highly infiltrative small, fused glands should be a clue as to the high-grade nature of the carcinoma.

3- Prostatic carcinoma grade 5 (2 cases):

Only 2 cases were of this grade. This is the most poorly differentiated pattern of prostatic carcinoma; pattern 5 resembles with smooth, rounded masses, cords of carcinoma. The necrosis is typically central, being surrounded by papillary, cribriform, or solid masses of carcinoma (Figure 4A and B).

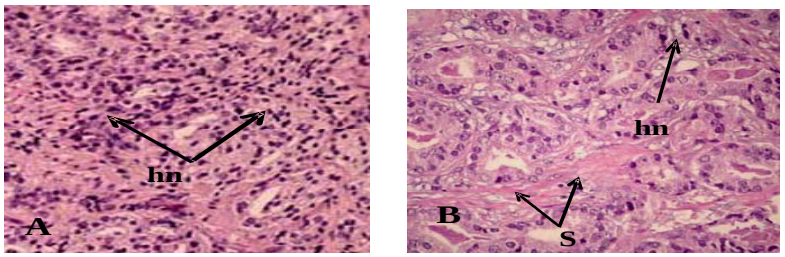

Figure (2 A and B): Light microscope of prostate adenocarcinoma, Gleason grade of 3 moderately differentiated gland patterns (400X) S =There is some stroma intervening the small glands - hn=hyperchromatic nuclei

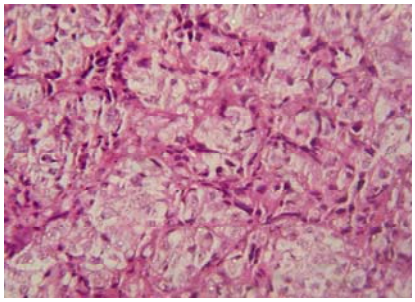

Figure (3): Light microscope of adenocarcinoma of prostate Gleason grade 4 with poorly differentiated gland pattern, (400X) H&E stained section.

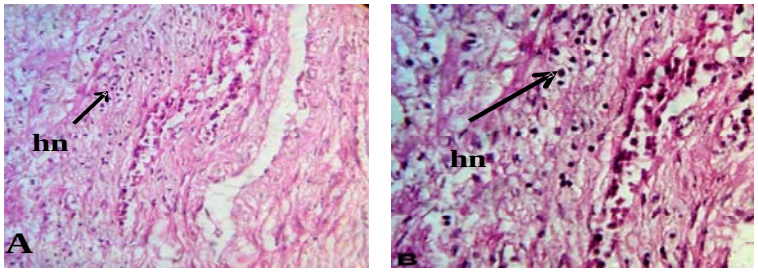

Figure (4 A and B): Light microscope of adenocarcinoma of prostate, Gleason grade 5 with very poorly differentiated gland pattern. Hn= hyperchromatic nuclei.

Relationship between growth hormone level and prostate carcinoma and benign hyperplasia

The level of GH was significantly enhanced ($P < 0.05$) in patients with PCa and BPH as compared to control group. However no significant differences ($P > 0.05$) were observed in the level of GH concentration between PCa and BPH Table (1).

Table (1): Level of serum GH in different studied groups (Means ± S.E).

Groups	Number	GH (ng / ml)		Level of significance
		Mean	± S.E	
Control	10	0.1064[a]	0.0128	
PCa	10	0.6707[b]	0.1846	P< 0.05
BPH	30	0.6853[b]	0.0969	P< 0.05

Different letters indicate statistically significant differences (p values < 0.05).
Similar letters indicate no significant differences.

The relation between Insulin-like growth factor - one and prostate carcinoma and benign hyperplasia

Mean serum level of IGF-I in patients with PCa was statistically significantly ($P<0.05$) higher (276.132±13.555 ng/ml) than both control groups (62.939 ± 6.654 ng/ml) and BPH patients (136.181±6.107 ng/ml). While, the level of this growth factor showed no significant differences ($P > 0.05$) in BPH patients as compared with control group table (2).

Table (2): The level of serum IGF-I in different studied groups (Means ±S.E).

Groups	Number	IGF-1 (ng/ml)		Level of significance
		Mean	± S.E	
Control	10	62.939[a]	6.654	
PCa	10	276.132[b]	13.555	P< 0.05
BPH	30	136.181[c]	6.107	P< 0.05

Different letters indicate statistically significant differences (p values <0.05).
Similar letters indicate no significant differences.

The relation between serum Insulin-like growth factor - one with age in prostate carcinoma patients

The present study demonstrated that the association between serum IGF-I levels and PCa was stronger in age 60 and declined as the age increased and this association was differed significantly ($P< 0.05$) at the 95% confidence level as shown in Table (3).

The relation between serum IGF-I with Gleason grade in PCa patients

In concern to the histological grade, IGF-I showed no significant differences with the progression of Gleason grade ($p=0.894$) at the 95% confidence level. IGF-I which is important for the occurrence of clinical PCa, did not appear to differentiately affect progression of most advanced stages of the disease, so there was no association between IGF-I and tumor grade in data of this study (Table 4).

Table (3): The association between ages with increased serum IGF-I in PCa patients

Patients Number	Age	IGF-I (ng/ml)
1	85	206.316
2	77	238.961
3	74	240.156
4	72	248.059
5	69	263.043
6	72	289.412
7	69	290
8	65	309.412
9	62	364.706
10	60	438.235
R	0.638	
P value	0.047	

Table (4): The association between Gleason grades with increased serum IGF-In PCa patients.

Patients Number	Gleason Grade	IGF-I (ng/ml)
1	5	206.316
2	4	238.961
3	4	240.156
4	4	248.059
5	3	263.043
6	3	289.412
7	4	290
8	4	309.412
9	5	364.706
10	3	438.235
R	0.069	
P value	0.894	

Discussion

Prostate cancer is the second most common cause of cancer deaths in men in most developed countries, and the incidence has increased significantly over recent years.

Pathological abnormalities occur more frequently within the prostate gland than any where else in the male human. On the basis of detailed pathologic studies, it was concluded that the initial lesion of BPH was a stromal nodule that induced the subsequent proliferation and organization of epithelial cells into new glandular elements (acini). It was thought that any glands in the prostate could be involved in the process and that wherever a fibromyomatous nodule appeared, the adjacent epithelium would penetrate it (McNeal, 1978), and these findings are in agreement with the results of the present study that the histological examination showed hyperplasia of both prostatic glandular and stromal elements. Also the results of the current study are in agreement with those of McNeal, (1988) who demonstrated that the initial microscopic nodules undergo further hyp erplasticchanges, increasing substantially in size. Microscopic nodules develop into macroscopic nodules. As this process occurs, the original anatomy of the prostate gland becomes markedly distorted; the true prostatic tissue is displaced caudally and posteriorly to form the peripherally located "surgical" capsule of the prostate.

The histological studies o f t h e prostatic carcinomas s a m p l e s showed small acini arranged in a variety of architectural patterns with cytological atypical, at least focal nucleolar prominence and absence of surrounding basal cell layer on high power, similar results were also recorded by (Allen and Cameron, 2004). Tumor grade indicates the degree of malignancy and is based on the appearance of the tumor cells under the microscope.

In concern to histological grade, IGF-I which is important for the occurrence of clinical PCa, did not appear to differentiately affect progression of most advanced stages of the disease. Therefore, the present results showed there was no association between IGF-I and tumor grade. Wolk *et al*., (1998), suggested that although important role of IGF-1, in the occurrence of clinical PCa, but it does not appear to differentially affect progression to more advanced stages of the disease

The results of the present study showed that the, the significant increaseing ($P< 0.05$) in GH levels in patients with PCa was strongly implicates GH/IGF-I axis as a risk factor for PCa, There was also a significant association between GH levels in patients with BPH comparing with control group. So, these results indicate that GH implicated in the development and subsequent functions of prostate gland. These result was in agreement with Reiter *et al.,* (1992), w h o reported that GH have a role in prostate development, and functions as it stimulates mRNA for IGF-I and its receptor in the prostate. Wang *et al*., (2005) also, demonstrate that the disruption of GH/IGF-I axis can inhibit the proliferation of advanced human PCa both *in vivo* and *in vitro*. Rick *et al.,* (2012) investigate the role of GHRH as an autocrine growth factor in PCa and they suggest that antagonists of GHRH should be considered for further development as therapy for PCa.

The results of the present study also showed that the level of IGF-I significantly increased in patients with PCa, t h i s r e s u l t indicate the direct relation between increasing levels of IGF-I with PCa risk. This result was in agreement with Nicole *et al*., (2003), who demonstrated that IGF-I play a role in the beast cancer and it could also be thought of as supportive for a similar link with respect to PCa. Generally, and as indicated by Cohen *et al*., (1991), the biologic role of IGF-1 is complex, because both normal and malignant prostate cells produce not only IGF-1, but also several of its binding proteins. The effects of IGF-I as mitogenic and antiapoptotic agents may be modulated by concentrations of IGF binding protein (IGFBP-3) in the peripheral circulation. Since increases in serum IGFBP-3 levels attenuating the mitogenic and antiapoptotic effects of IGF-I in tissues. IGF-I is able to stimulate or activate androgen receptor, resulting in PSA production. PSA cleaves IGFBP-3 specifically resulting in a greater level of free IGF-I to induce a resistance to apoptosis in PCa cells and increasing in mitosis (Djavan *et al*., 2001). Chan *et al*. (1998), reported that every 100 ng/ml increase in circulating IGF-I concentration may correspond to an approximate doubling of the

risk of PCa.

In prostate gland, epithelial and stromal proliferation increase in many older ages and this proliferation is due to the role of IGF-I in stimulating the proliferation of epithelial cells within the prostate, therefore, the IGF-I induction of epithelial proliferation would increase the number of cells at risk to develop cancer (Yu and Rohan, 2000; Oliver *et al*., 2004). IGF-I have been shown to protect cells from undergoing apoptosis through an IGF-IR mediated cell survival pathway. This mean IGF-I stimulates DNA synthesis and cell replication by causing cells to traverse the successive phases of the cell cycle, thus acting as a progressive factor during cell cycling. Androgens stimulate the cell transition from G0 to G1 phase, making them responsive to IGF-I which then facilitate the progression from G1 into the S phase which allows progression and continuation through the cell cycle, resulting in DNA synthesis and cell proliferation (Djavan *et al*., 2001).

Sex steroids can modulate the GH/IGF-I axis at many levels. Steroids can directly affect pituitary GH secretion; they can affect IGF-I levels by altering production directly or by altering levels of IGF-binding proteins and hence affecting clearance (Djavan *et al*., 2001). The important influence of the GH/IGF-I axis in cancer development and behaviors reflects its endocrine actions, although autocrine and paracrine actions of IGF-I are important for normal growth and development (LeRoith *et al*., 2001).

The results of the present study indicated that there was significant association between serum level of IGF-I and patients with BPH comparing with controls and between patients with BPH and PCa patients concerning serum IGF-I level. Monti *et al*., (2001) reported that, although androgen involved in the generation of BPH, though androgen stimulation alone does not completely explain the development of BPH. Probably because androgen action is only in part direct and is mainly indirect through prostatic production of some growth factors like IGF-I. These locally produced peptides are considered to be autocrine and/or paracrine mediators of the stromal-epithelial interaction. Abnormal synthesis and secretion of these peptides may be related to the inductive embryonic capacities of the stroma. Ramsay and Leung in (2009) also reported that androgen deprivation reduces tumor activity in approx. 80% of patients with advanced disease, but most tumors relapse within 2 years to an incurable hormone-resistant state. Even for patients with early disease at the time of diagnosis, a proportion of patients will unfortunately develop relapsed disease following radical therapy.

The present study demonstrated that the association between serums IGF-I levels and PCa was stronger in age 60 and declined as the age increased. This result is in agreement with the study of Chan *et al*., (1998) and Wolk *et al*., (1998), they examined the association of IGF-1 levels with PCa risk among men younger than 70 year. They found that the risk of PCa among persons younger than 70 years was stronger.

In conclusion it's appeared that IGF-I play an important role in the etiology of PCa and BPH.

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کورتیا لێکولینێ:

ئەنجامەکانی زیندە لابراوەکان دەریانخست کە 10 بار وەکو شێرپەنجەی پرۆستات PCa بە پلەی جیاواز (3،4 ، 5) دەستنیشانکران و 30 باریش وەکو فرە خانەیی پاکی پروستات BPH دەستنیشانکران.

بە بەراورد کردن لە گەل بەهاکانی کونترولدا ئاستی (P<0.05) GH لە نەخوشەکانی شێرپەنجەی پرۆستاتدا بە شێوەیەکی بەر چاو بەرز بوو لە کاتێکدا ئاستی (P<0.05) GH لە نەخوشەکانی فرە خانەیی پاکی پروستات نزمتربوون بە بەراورد لە گەل هی کونترول و ئەو نەخوشانەی کە شێرپەنجەی پرۆستاتیان هەبوو بەر چاویش نەبوو.

هەروەها ئامارییەکانیش ئاماژەیان بەوە دا کە ئاستی (P<0.05) – IIGF لە سیرمدا بەرزتر بووە هەروەها بە شێوەیەکی بەرچاو پێوەند بوو بە شێرپەنجەی پروستاتەوە لەو نەخوشانەی کە شێرپەنجەی پروستاتیان هەبوو بە بەراورد لە گەل ئاستی IGF-I ی سیرەمی کونترولەکاندا کە لە ناو پیاوانی گەنجتر لە 70 سال لەهی بە تەمەنترەکان بەهێزتر بوو (P=0.000038) بەلام IGF-Iی سیرەم ئەوەی پیشاندا کە جیاوازی بەر چاولە نێوان کونترول و ئەو نەخوشانەی کە فرە خانەیی پاکی پروستات BPH یان هەبوو نەبوو بەلام ئاستی IGF-I بە شێوەیەکی بەرچاو (P<0.05) نزمتر بوو لەو نەخوشانەی کە فرە خانەیی پاکی پروستاتیان هەبوو بە بەراود لە گەل ئەوانەی شێرپەنجەی پروستاتیان هەبوو.

الخلاصة

تم إجراء هذا البحث لغرض دراسة دور هرمون النمو في فسلجة أمراض البروستات، ودور عامل النمو شبيه الأنسولين –1 كعامل خطورة في الذكور المسنين المصابين بمرض سرطان البروستات وورم البروستات الحميد. استخدم لهذا الغرض (40) مريض مصابين بسرطان البروستات وورم البروستات الحميد تراوحت أعمارهم بين (54–85 سنة)، وعشرة أشخاص كمجموعة سيطرة (47–75 سنة) والذي تم تأكيدهم بواسطة ألاختبار ألمستقيمي(DRE) ومستوى المستضد النوعي للبروستات (PSA). تم أخذ عينات الدم والأختزاعات من جميع المرضى، بينما لمجموعة السيطرة، تم أخذ عينات الدم فقط. وقد تم تحديد نمط نمو وتدرج الخلايا السرطانية بالمقاطع النسجية المصبوغة بصبغتي الهيماتوكسالين والايوسين باستخدام نظام تدرج كليسون. وتم قياس مستوى كل من هرمون النمو وعامل النمو شبيه الأنسولين–1 في مصول جميع المرضى ومجموعة السيطرة بواسطة تقنية الـ(EISA). أظهرت نتائج التشخيص النسجي للأختزاعات الكشف عن عشر حالات سرطان البروستات (بتدرج 3،4،5) بالاعتماد على خمسة أنماط من النمو النسجي، وثلاثون حالة من ورم البروستات الحميد. مقارنة بقيم مجموعة السيطرة، كان مستوى هرمون النمو عالي معنويا" (P< 0.05) في مصول مرضى السرطان وورم البروستات الحميد، بينما لم تكشف الدراسة عن وجود اختلاف معنوي بين مستوى هذا الهرمون في كل من مصول مرضى سرطان البروستات ومصول مرضى ورم البروستات الحميد. أشارت نتائج التحليل الإحصائي أيضا إلى إن مستوى عامل النمو شبيه الأنسولين –1 كان عالي معنويا" (P< 0.05) بكثير في مصول مرضى سرطان البروستات مقارنة مع مستواه في مصول السيطرة. كذلك اظهر مستوى عامل النمو شبيه الأنسولين–1 فرقا" معنويا" بين (مرضى ورم البروستات الحميد مع السيطرة) وبين (مرضى السرطان ومرضى ورم البروستات الحميد). أوضحت نتائج الدراسة الحالية بان العلاقة المعنوية بين مستوى عامل النمو شبيه الأنسولين–1 ي ومرض سرطان البروستات كان أقوى (P=0.047) في عمر 60 سنة ولكن مستواه بدأ بالنقصان مع تقدم العمر، بينما لم تظهر الدراسة وجود علاقة معنوية(P=0.854) بين ازدياد مستوى عامل النمو شبيه الأنسولين–1 مع تقدم مراحل المرض استنادا" الى (تدرج كليسون). نستنتج من هذه الدراسة بان لعامل النمو شبيه الأنسولين –1 دور مهم في تحديد أسباب أمراضية سرطان البروستات وورم البروستات الحميد.