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Over-expression of β-catenin is associated with high grade of prostatic cancer in Libyan patients

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Abstract

Objectives: At present, sufficient prognostic markers for prostate cancer (PCa) progression are still lacking, in spite of thorough investigation. The aim of this study was to evaluate abnormalities of β-catenin protein expression, subcellular localization and determine its relation to different clinicopathological features and disease free survival in prostate cancer patients.

Patients and methods: Forty prostate cancer specimens, obtained from patients with different stages of prostate cancer (83% stage IV) who underwent a radical prostatectomy or TURP flanked by 2006 and 2011, β-catenin was determined by immuno-histochemistry (IHC). The membranous expression was semi-quantitatively evaluated in four scores (0, 1+, 2+, 3+). Clinical records of these patients were studied for follow up data.

Results: β-Catenin immune staining results show over-expression of β-catenin in PCa Libyan patients. There was no statistically significant difference in β-catenin immune expression as regards histopathological type, perineural invasion, tumor stage, biological recurrence. However, β-catenin over-expression showed significant correlation with old age (p < 0.014).

Conclusions: We concluded that changes in expression and cell distribution of β-catenin correlated with the progression degree of prostate adenocarcinoma, signifying a role of this molecule as a marker of progression and prognosis. Further investigations, on a larger and more heterogeneous population, should be carried out to validate and extend our results.

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Introduction

Prostate cancer (PCa) is the second most common cause of cancer and the sixth leading cause of cancer deaths among men worldwide with an estimated 899,000 new cases and 258,000 new deaths in 2008. The global PCa burden is anticipated to grow to 1.7 million new cases and 499,000 new deaths by 2030 basically due to the growth and aging of the global population [1]. Recent statistics reveal that PCa continues to remain the most commonly diagnosed lethal malignancy in men in the United States with 1 out of 6 men developing PCa and 1 out of 35 dying from it [2].

There are now more than 240,000 men in the United States diagnosed with PCa each year [3], and 90% of PCa are clinically localized and occult disease at time of diagnosis [4].

In patients with localized PCa, the 5-year survival approximates 100%; however, in patients in whom distant metastasis have occurred, the 5-year survival drops to 31% [5]. Like most other solid malignancies, PCa can metastasize to distant organs such as the liver, lungs and brain, but it has an extraordinarily high propensity for metastasizing to the bone. In one autopsy study, ~80% of the men who had died from PCa possessed bone metastasis [6].

Gleason grade is one of the most widely used grading systems for predicting the progression of PCa. A more aggressive disease is associated with higher Gleason sum scores. Nevertheless, the pathological grade, serum Prostate Specific Antigen (PSA) value and clinical stage have some restrictions that hinder evaluation of the prognosis of PCa, although the PSA level combined with the Gleason grading system is still considered the most reliable prognostic marker [7,8]. Presently, adequate prognostic or predictive markers for tumor progression are still deficient. However, some molecules are involved in diverse processes such as cell proliferation, apoptosis, cellular adhesion, tumor suppression and cell cycle-related factors have been linked to PCa outcome [9,10].

Several genes and signaling pathways have been implicated in PCa initiation and progression, such as p53, C-MYC, Nkx3.1, PTEN, androgen receptor (AR), and Wnt/β-catenin [11]. Wnt/β-catenin signaling has been implicated in both normal prostate development and in PCa progression [12]. β-Catenin forms part of the adherent junction with E-cadherin and is also a component of canonical Wnt signaling. However, the function of β-catenin in human PCa is unclear [13]. It has been observed that β-catenin expression and localization change during human PCa progression. However, results are inconsistent. Several studies have seen an increase in β-catenin expression and nuclear localization in late stage cancer samples, while others have reported a loss in nuclear expression in advanced tumors [14–18].

In the current study, we examined the expression of β-catenin in a series of Libyan PCa by IHC. We tried to determine its value as predictive marker for metastatic potential. Additionally, the relationship between this molecular marker and known prognostic factors of serum PSA and Gleason grade was evaluated.

Patients and methods

Clinicopathological features and follow up data

Archival samples of 40 prostatic adenocarcinoma were examined in the present study. All the tumor samples were collected from Pathology Department, Faculty of Medicine, Benghazi University between January 2006 to December 2011 depending on accessibility of representative paraffin blocks.

The patient's clinical files were read in the hospital archives in order to gather the appropriate clinical information and follow up data for current study. For each patient, we obtained the following information: age, histological diagnosis, grading, staging, pre-treatment PSA level, date of diagnosis, treatment, cause and date of death. All patients were followed up until death or when last seen alive at their clinical visit (Dec-2012) with the mean followup time of 25 months (range: 6–72 months). The duration of follow-up was determined for each patient from hospital and clinic charts.

Clinical stages were determined according to the International Union against Cancer (UICC) classification of 2009. Clinical staging routinely included abdominal and pelvic computerized tomography (CT), chest radiograph or thoracic CT, isotope bone scanning, and extended/extensive prostate biopsy, as described elsewhere. PSA levels at diagnosis ranged between 0.1 and 500 ng/ml (mean: 113 ng/ml), and Gleason score at biopsy ranged between 6 and 10.

A skilled pathologist confirmed all diagnosis, and the following histopathological features were recorded which include; histological type, histological grading determined in accordance with the Gleason grading system, lymphovascular invasion, perineural invasion. All tumors were classified using the histopathological criteria of WHO classification. The key clinicopathological data of patients are summarized in Table 1.

Immuno-histochemical method
β-Catenin immunostaining

Paraffin embedded blocks of PCa have been obtained from pathology department archive. Sections were cut in sequence at 5 μm for immune-histochemical staining. IHC analysis has been done using the automatic system (Bench-Mark XT, Ventana Medical System, Inc., Tucson, Arizona, USA). This fully automated processing for bar code labeled slides included baking of the slides, solvent free deparaffinization, antigen retrieval in a cell conditioning buffer CC1 (Mild: 36 min conditioning, and standard: 60 min conditioning), incubation with Mouse monoclonal anti-β-catenin antibody (clone: 4, isotype: IgG1, Catalog no.: 760-4242 Ventana Medical Systems), for 32 min at 37 °C. Application of ultra-view TM universal DAB has been applied. Ultra view DAB includes: ultra-view universal HRP, ultra view universal DAB inhibitor, ultra view universal DAB chromogen, ultra view universal DAB H2O2, and ultra view universal DAB copper. Counterstaining with haematoxylin (2021) for 4 min, and post-counterstaining with bluing reagent (2037) for 4 min. After staining, the sections were dehydrated in ethanol, cleared in xylene, and covered with Mountex and cover slips.

Evaluation of β-catenin staining

The assessment of staining was performed with a light microscope at the magnification of ×40, blinded by the information on tumor grade, stage or clinical outcome. Membranous and cytoplasmic staining was evaluated separately. For cell membrane staining, four categories were used, (+++, ++, +, 0), where 0: no expression, no detectable staining in <10% of the membrane, +: weak but detectable discontinuous staining present in 10–39% of the membrane, ++: moderate, clearly positive discontinuous staining present in 40–90% of the membrane, and +++: intense continuous staining

Table 1 Clinicopathological characteristics of the patients with PCa.

Characteristic		No. of patients	Percentage (%)
Age (years)	≥74	23	57.5
	<74	17	42.5
Type of biopsy	Core biopsy	31	77.5
	TURP	8	20
	Radical prostatectomy	1	2.5
Histopathological type	Acinar adenocarcinoma	39	97.5
	Ductal adenocarcinoma	1	2.5
Pre-treatment PSA level mean (range)		112 (0.1–500)	–
Gleason score	6	2	5
	7	12	30
	8	8	20
	9	11	27.5
	10	7	17.5
Histological grade	Grade II (5–7)	14	35
	Grade III (8–10)	26	65
Perineural invasion	Yes	9	22.5
	No	31	77.5
Lympho/vascular invasion	Yes	3	7.5
	No	37	92.5
Clinical stage	II–III	7	17.5
	IV	33	82.5
Metastasis	Yes	33	82.5
	No	7	17.5
Site of distant metastasis	Bone	29	87.87
	Liver	2	6.06
	Bone and others (lung, liver, pancreas)	2	6.06
Biological recurrence	Yes	14	35
	No	19	47.5
	Unknown	7	17.5
Status at end point	Dead	21	52.5
	Alive	12	30
	Unknown	7	17.5

of the membrane creates a honeycomb pattern. The cytoplasmic staining was also graded into four categories where 0: negative, no detectable staining, +: weak, but detectable still staining, ++: moderate, clearly positive but still weak, +++: heavy staining, intense. The membrane index (MI) was calculated with both the intensity of staining and fraction of positively-stained cells taken into account using the following formula:

$$I = 0 \times f0 + 1 \times f1 + 2 \times f2 + 3 \times f3$$

where I is the staining index, f0–f3 are the fractions of the cells showing a defined level of staining intensity (from 0 to 3). Theoretically, the index could vary between 0 and 3 [19,20]. The reproducibility of the β-catenin staining indices was tested twice by one of the observers (AE) analyzing the sections, after a few days (intra-observer variation).

Statistical analysis

Statistical analysis was performed using the SPSS® (SPSS, Inc., Chicago, USA) and STATA (Stata Corp., TX, USA) software pack-

ages (SPSS for Windows, version 18.0.3 and STATA/SE 11.1). Frequency tables were analyzed using the Chi-square test, with the likelihood ratio (LR) or Fisher's exact test being used to assess the significance of the correlation between the categorical variables. Differences in the means of continuous variables were analyzed using non-parametric tests (Mann–Whitney) or Kruskall–Wallis for 2- and K-independent samples respectively. Analysis of variance was only used to derive the mean values (and 95% CI) of each individual stratum. Univariate survival analysis for the outcome measure [disease-specific survival (DSS) and disease-free survival (DFS)] was based on the Kaplan–Meier method, with log-rank (Mantel–Cox) comparison test. In all tests, $p < 0.05$ was regarded as statistically significant.

Results

Expression patterns of β-catenin

The expression pattern of β-catenin was predominantly membranous, in normal prostatic glands, hyperplastic prostatic glands and in tumor area as well. The expression patterns of β-catenin in PCa lesions are illustrated in the following figures respectively

Table 2 Expression of β-catenin in Libyan PCa patients as related to clinicopathological data and disease outcome.

Features		Number (%)	β-Catenin expression (%)		p-Value
			Below mean = 0	Above mean = 1	
Age	≥74	18 (45)	5/19 (26.3)	13/21 (61.9)	0.024
	<74	22 (55)	14/19 (73.7)	8/21 (38.1)	
Type of biopsy	TURP	31 (77.5)	14/19 (73.7)	17/21 (81.0)	0.55
	Core biopsy	8 (20)	4/19 (21.1)	4/21 (19)	
	Radical prostatectomy	1 (2.5)	1/19 (2.5)	0 (0)	
Diagnosis	Acinar adenocarcinoma	39 (97.5)	19/19 (100)	20/21 (95.2)	0.525
	Ductal adenocarcinoma	1 (2.5)	0 (0)	1/21 (4.8)	
Histological grade	Grade II	14 (35)	10/19 (52.6)	4/21 (19.0)	0.014
	Grade III	26 (65)	9/19 (47.4)	17/21 (81)	
Perineural invasion	Yes	9 (22.5)	4/18 (22.2)	5/22 (22.7)	0.970
	No	31 (77.5)	14/18 (77.8)	17/22 (77.3)	
Lymphovascular invasion	Yes	37 (92.5)	1/19 (5.3)	2/21 (9.5)	0.609
	No	3 (7.5)	18/19 (94.7)	19/21 (90.5)	
Metastasis	Yes	33 (82.5)	15/19 (78.9)	18/21 (85.7)	0.574
	No	7 (17.5)	4/19 (21.1)	3/21 (14.3)	
Biological recurrence	Yes	13 (40.6)	7/16 (43.75)	10/16 (62.5)	0.719
	No	19 (59.4)	9/16 (56.25)	6/16 (37.5)	
Status at the end point	Alive	12 (36.4)	6/16 (37.5)	6/17 (35.3)	0.895
	Dead	21 (63.6)	10/16 (62.5)	11/17 (64.7)	

(Fig. 1a–d). The mean value of β-catenin staining index (MI) was 2.5.

Correlation of β-catenin expression with clinicopathological characteristics

The distribution of β-catenin expression in tumor sample in relation to clinicopathological characteristics is present in Table 2. Using different cut-off points mean, median, 3-tier score (0 vs 1, 2, 3), (0, 1 vs 2, 3) and (0, 1, 2, 3). An interesting finding in our immune-histochemical study, β-catenin over-expression (membranous) shows a significant correlation with the age (p < 0.024) in that tumors of old patients (≥74 years) (13/18) over-express β-catenin more than tumors of young patients (<74 years) (8/22). Moreover, over-expression of β-catenin (membranous) was also significantly (p < 0.014) associated with the higher grade (Gleason > 7) in that Gleason score >7 cancers (17/26) showed higher expression of β-catenin compared to Gleason score = 5–7 PCa (4/14).

There was no statistically significant difference in β-catenin immune expression as regards histopathological diagnosis, type of biopsy (core, TURP, radical prostatectomy), perineural invasion, lymphovascular invasion, tumor stage and recurrence.

Discussion

Wnt/β-catenin signaling plays a fundamental role in controlling an array of cellular processes, such as the determination of cell fate, cell proliferation, migration, and polarity, and the maintenance of stem cells. Various studies have reported that changes in Wnt signaling can lead to carcinogenesis and the progression of malignancies, including PCa [21–23]. In addition, some investigators have suggested that Wnt/β-catenin signaling and the AR play critical roles in PCa progression [23,24].

The role of β-catenin in prostate development is not known and its function in prostate cancer is not clearly defined [25]. Previous studies implicated β-catenin in the pathogenesis of PCa because it localizes in tumor-cell nuclei in 20–40% of castration resistant prostate cancer (CRPC) specimens [15,26,27]. More recently, a further group reported that activation of Wnt/β-catenin signaling is involved in PCa initiation and progression in a mouse model [12,28]. Collectively, these findings imply that the Wnt canonical pathway is implicated in the pathogenesis of a subgroup of advanced PCa.

It has been observed that β-catenin expression and localization change during human PCa progression, however, results are inconsistent [25]. Aberrant expression and localization of β-catenin in PCa are more common than predicted by Wnt pathway mutation [13,29]. Abnormal β-catenin expression was found in 23% of tumor samples from radical prostatectomy, and in 38% of CRPC samples, and correlates with high Gleason score [15]. However, the detection of nuclear β-catenin in hyperplasia and in advanced tumors suggests that activation of Wnt/β-catenin signaling has a role in the premalignant stages of the disease and in the progression to CRPC [30].

In this study, we examined the expression and localization of β-catenin protein in a subset of PCa and a number of adjacent histologically normal and hyperplastic mucosa. The results showed that a membranous staining pattern was well preserved in prostatic adenocarcinomas without detectable nuclear immuno-reactivity. This finding is consistent with those of previous studies in which no nuclear β-catenin immuno-staining was observed in prostatic adenocarcinomas [14,31].

An interesting finding in our immuno-histochemical studies is that the membranous over-expression of β-catenin staining occurs mainly in cases with higher Gleason scores (>7) prostatic adeno-
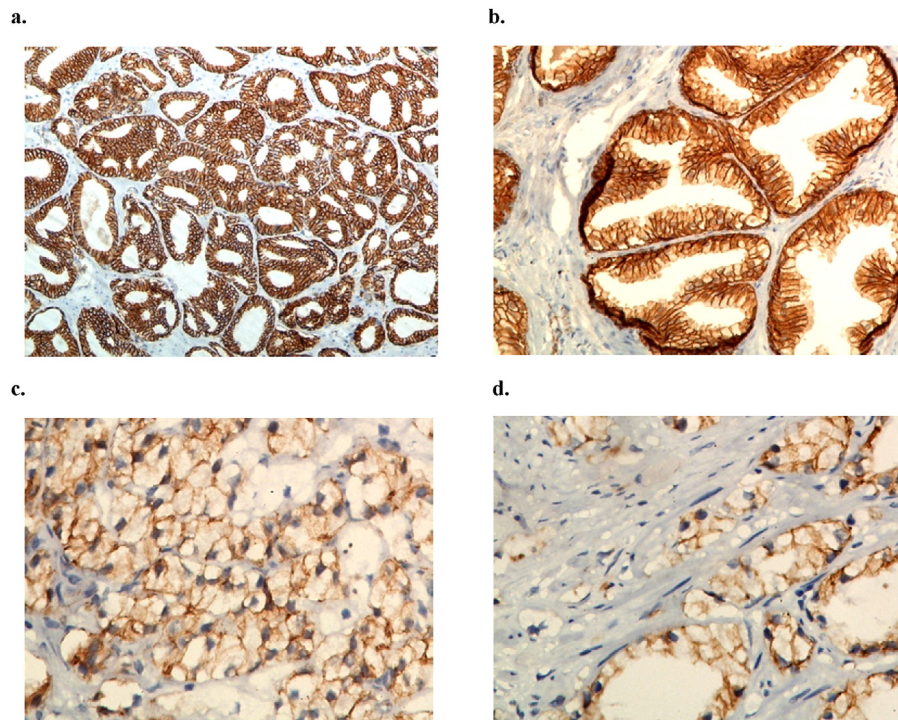
a.

b.

c.

d.

Figure 1   (a) Immunohistochemical staining of β-catenin. Membranous expression of β-catenin in bening prostatic hyperplasia (IHCX20) (Department of Pathology, Faculty of Medicine, Benghazi University). (b) Strong membranous β-catenin expression in pattern three prostatic carcinoma (IHCX20) (Department of Pathology, Faculty of Medicine, Benghazi University). (c) Moderate membranous β-catenin expression with weak membranous expression in some area of prostatic carcinoma (IHCX40) (Department of Pathology, Faculty of Medicine, Benghazi University). (d) Weak membranous β-catenin expression of prostatic carcinoma (IHCX 40) (Department of Pathology, Faculty of Medicine, Benghazi University).

carcinomas. This finding is consistent with finding of Whitaker et al. who observed that increased β-catenin expression in only high Gleason score (>7) prostate cancer and a gradual loss in nuclear distribution with increasing Gleason grade [17]. The same observation was established by Chen et al. who observed the high levels of Wnt-1 and β-catenin expression was linked with advanced, metastatic, hormone-refractory prostate carcinoma, in which they can serve as markers of disease progression [16]. On the other hand, Bismar et al. and Kallakury et al. have found that the loss of β-catenin was associated with high tumor grade [32,33]. Even though, few studies [18,34] have reported that there was no signification association between β-catenin expression and Gleason score.

This discrepancies between our results and other might be explained by the methodological differences in patient sampling, fixation and the protocols used for immunohistochemical techniques.

In the current study, we did not find any significant correlation between β-catenin expression and lymphovascular invasion. A similar finding has been reported by Morita et al. [14].

In conclusion we concluded that changes in expression and cell distribution of β-catenin correlated with the progression degree of prostate adenocarcinoma, suggesting a role of this molecule as marker of progression and prognosis, even if based on a restricted number of cases. Admittedly, supplementary studies on a larger cohorts and more heterogeneous population are necessary to validate and extend our results.

Conflict of interest

The authors state that no conflict of interest exists.

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Authors' contributions

These authors have contributed equally to the work.

Ethical Committee Approval

Approved

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