Biomarkers for Evaluation of Prostate Cancer Prognosis

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Abstract

Prostate cancer, with a lifetime prevalence of one in six men, is the second cause of malignancy-related death and the most prevalent cancer in men in many countries. Nowadays, prostate cancer diagnosis is often based on the use of biomarkers, especially prostate-specific antigen (PSA) which can result in enhanced detection at earlier stage and decreasing in the number of metastatic patients. However, because of the low specificity of PSA, unnecessary biopsies and mistaken diagnoses frequently occur. Prostate cancer has various features so prognosis following diagnosis is greatly variable. There is a requirement for new prognostic biomarkers, particularly to differentiate between inactive and aggressive forms of disease, to improve clinical management of prostate cancer. Research continues into finding additional markers that may allow this goal to be attained. We here selected a group of candidate biomarkers including PSA, PSA velocity, percentage free PSA, TGFβ1, AMACR, chromogranin A, IL-6, IGFBPs, PSCA, biomarkers related to cell cycle regulation, apoptosis, PTEN, androgen receptor, cellular adhesion and angiogenesis, and also prognostic biomarkers with Genomic tests for discussion. This provides an outline of biomarkers that are presently of prognostic interest in prostate cancer investigation.

Keywords: Biomarkers - prostate cancer - PSA - prediction of prognosis

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Introduction

One of the most important health problems in men is prostate cancer (Howlader et al., 2011). Predominantly it is an older men disease as the rate of prostate cancer increases significantly after of 40 year and about two-thirds of all prostate cancers occur in men 65 and older (Howlader et al., 2011; Timothy Wilt, 2013). It is estimated 307,000 men died due to prostate cancer in 2012 in worldwide (UK, 2012). Incidence and mortality of prostate cancer in most native Asian population progressively raised, but are approximately one-third lower in corresponding Asian-American cohorts, which are themselves less than the rates in other corresponding American cohorts (Ito, 2014). Generally, incidence rate in more developed regions is obviously greater than less developed regions (Globocan, 2012).

Genetic and environmental factors, especially a western diet could partially describe these differences. Of course lower exposure to prostate-specific antigen (PSA) screening program in Asian people might be an important factor (Ito, 2014). This disease has various features contain slow-growing tumor with no clinical consequence, or develops rapidly which lead to aggressively metastatic and lethal outcome (Cary and Cooperberg, 2013). Prostate cancer, with a lifetime prevalence of one in six men, is the second cause of death and the most prevalent cancer in men (Panjehpour et al., 2012). This cancer has an important role in morbidity and mortality of men.

The symptoms of prostate cancer are infrequent at the time of diagnosis, because of local growth of the tumor, symptoms of urinary obstruction like decreased urinary stream, urgency, hesitancy, nocturia and incomplete bladder emptying may occur. These nonspecific symptoms are more indicative for benign prostatic hyperplasia (Lawrence, 2011).

Prostate cancer risk factors may be divided two categories: exogenous and endogenous, albeit some factors are not solely one or the other such as race, aging, oxidative stress. Endogenous risk factors are included aging and oxidative stress, family history, and race (the risk of prostate cancer is higher in African-American races than the other races) and hormones as altered androgen metabolisms may have significant role in prostate cancer. Endogenous and exogenous factors may have effect on hormonal levels (Bostwick et al., 2004). Some of exogenous risk factors are including rich fat diets particularly poly unsaturated fat, vitamin deficiency especially vitamin D and E (Garg et al., 2014), beside fruits and vegetable intake may decrease prostate cancer risk (Askari et al., 2014), environmental agents such as endocrine disrupting chemicals-EDCs (Euling and Kimmel, 2001), cadmium, occupational factors (Doolan et al., 2014), like farming or working in the rubber industry. Other factors included smoking, energy intake, vasectomy, physical activity and anthropometry (Bostwick et al., 2004).

Currently screening has an important role in prostate...
cancer diagnosis and PSA test is the most greatly noninvasive screening tool which causes enhanced detection at earlier stage and decreasing in the number of metastatic patients but because of low specificity of PSA, unnecessary biopsies and error diagnose is performed (Euling and Kimmel, 2001; Cary and Cooperberg, 2013).

As noted above prostate cancer has various features, so the prognosis following diagnosis is greatly variable (Bickers and Aukim-Hastie, 2009). Some patients have inactive form of disease with no important effect on mortality for 15 years, on the others some patients have aggressive form of the disease as metastasis may occur during 2 years (Siddiqui et al., 2004); metastasis has important role in cancer mortality (Bickers and Aukim-Hastie, 2009). There is requirement for new and high sensitive prognostic biomarkers to improve clinical management of prostate cancer particularly can differentiate between inactive and aggressive form of disease. The researches continue for finding additional markers that provide these goals (Ramirez et al., 2008). For new therapeutics, it is necessitate developing more reliable biomarkers. Currently, many prostate cancer biomarkers have been identified and are investigating (Bensalah et al., 2007). This short review mainly depicts studies that have researched new biomarkers and introduced new viewpoints on prognostic biomarkers of prostate cancer and illustrating their benefits and limitations (Table 1). This paper is neither intended to be a comprehensive depiction of the individual biomarkers nor including list of all available biomarkers because the list of biomarkers is in evolvement and finding is beyond that described here.

Characteristics of Biomarkers

Biomarker (biological marker) is a molecule that can be measured and evaluated as an indicator of normal biological, pathological processes or pharmacological response to a therapeutic intervention (Ilyin et al., 2004). An ideal biomarker has multiple characteristics:

i) Disease-specific;
ii) Slightly invasive;
iii) Cost-effective;
iv) Reproducible assay with sufficient sensitivity and specificity;
v) Perfectly with correlation to disease outcome (Lin, 2009).

Cancer biomarkers are generally grouped into three categories: prognostic, predictive, pharmacodynamic. Prognostic biomarkers predict the natural course of cancer and to recognize tumor’s outcome. Predictive biomarkers assess possible advantage of a special treatment. Therapeutic impacts of a drug on a tumor are evaluated by pharmacodynamic biomarkers, these biomarkers perhaps determine the suitable dosage of a novel anticancer drug in the early steps of clinical progression (Madu Co, 2010).

Prostate-Specific Antigen (PSA)

PSA is a kallekrein-like serine protease secreted by the epithelial cells of prostate and encoded by an androgen-responsive gene (19q 13.3-13.4) (Rigman et al., 1989). The major role of PSA is liquefying of human semen by its proteolytic function (Lin, 2009; Madu Co, 2010). Serum PSA level is age and race dependent. Age specific range of PSA in different races indicated in table-2 (Zorn KC, 2014). It is reported that if the upper limit of normal PSA increases in men aged 60-69 years (4.5ng/ml), an important loss in sensitivity occurs (Bassler Tj Jr and O’Dowd Gj, 1998). Routinely, PSA is the only biomarker that is used for diagnosis and prognosis of prostate cancer (Rittenhouse et al., 1998). The extensive use of the PSA test increased detection of disease at earlier stages (Ilyin et al., 2004), which caused a decrease in number of patients in metastatic state (Shariat et al., 2008a). Because high levels of PSA are found in more progressive stages and more unfavorable result, this biomarker has been used as a staging and prognostic tool (Shariat and Kevin, 2004).

In spite of this significant role, PSA is organ-specific but not cancer specific. The serum PSA level increases in benign prostatic hyperplasia (BPH: increase in size of prostate secondary to a noncancerous proliferation of prostate gland cells) (Charrier et al., 2001), prostatitis (inflammation of prostate) (Tricoli et al., 2004), following interventions like biopsy (Yuan et al., 1992), also in older age, ejaculation (16) and use of specific drugs such as male hormones. On the other hand, numerous factors may cause decrease in PSA level such as 5-α reductase inhibitors, herbal mixtures, obesity, aspirin, statins, thiazide diuretics (Society, 2013). Hence false positives are a major difficulty for PSA test. This unspecificity has led to the over diagnosis of inactive disease (Etzioni et al., 2002), but upper limit 4ng/ml eliminates the majority of prostate cancers (Shariat et al., 2008a). The studies indicated that cut off 4.1ng/ml can distinguish only 20.5% of prostate cancer cases (Thompson et al., 2005). Recent data indicated that considerable number of men had prostate cancer within normal range of PSA and importantly many of these patients were found to be high grade (Lin, 2009). The association between total PSA and prostate cancer has impaired over the last 20 years (Stamey et al., 2002; Shariat et al., 2006). In order to increase PSA diagnostic specificity and prognostic ability, several parameters of PSA have been used.

PSA Velocity (PSAV)

PSAV, sequential evaluation of PSA levels over time (Sardana et al., 2008) or ratio of increase of PSA before diagnosis, has been found to be an independent predictor of return of disease after radical prostatectomy (Patel et al., 2005). The studies revealed that BPH patients had a linear increase in PSA level over time, while prostate cancer patients had a first increase following by an exponential rise which occurred 5 years before cancer detection (Shariat et al., 2008a). Some studies indicated that PSA velocity >2ng/ml per year pre diagnosis, associated with a shorter disease-free survival time in spite of radical prostatectomy (D’Amico et al., 2004). The specificity of PSAV is high but its sensitivity is so low that couldn’t inescapable prostate biopsy in a patient with increased PSA level, another limitation is as a result of biological and analytical variation (such as PSA stability, PSA measuring differences) that cause day-to-day variation in PSA level
and eventually imprecision of PSA velocity (Nixon et al., 1997). It is recommended that PSAV may be useful in patients with normal serum PSA level at the beginning of screening, but it is less beneficial in deciding whether patients with a serum PSA level of 4-10 ng/ml must be biopsied (Shariat et al., 2008a). The researchers defined “PSAV risk count”, a new way to assess PSA dynamic which computed by counting the number of times that PSAV goes beyond a particular threshold value (Carter Hb, 2007). The studies indicated that PSAV risk count may decrease unnecessary prostate biopsies and diagnoses low-risk prostate cancer (Loeb et al., 2012).

**Percentage Free PSA**

Serum PSA is in several molecular forms and complexes PSA (bound to protease inhibitor such as α1-antichymotrypsin, α1-antitrypsin, α2 macroglobulin) (Shahrokhi F Shariat and Kevin, 2004). Free PSA comprises 5-45% of total PSA, percentage of free PSA (%Free PSA) calculated by free PSA/total PSA *100 (Shariat et al., 2008a). The use of %Free PSA has been certified as an appendix to total PSA testing in men with a serum total PSA level of 4-10 ng/ml (Shariat et al., 2008a). The researchers suggested free PSA as a late-stage predictor of prostate cancer (Finne et al., 2008). It seems that %PSA is inversely associated with risk of finding prostate cancer in biopsy (Bickers B, 2009). The association of free-total PSA ratio in men with PSA levels of 2.1-10.0 ng/ml and probability of prostate cancer indicated in table-3 (Kitagawa et al., 2014). It is indicated that %free PSA is significantly low in aggressive disease conditions like Gleason score≥7, metastases, positive surgical margins (Catalona et al., 1998). It is noted that Gleason score is a prognostic grading system based absolutely on histological pattern on differentiation and organization of carcinoma cells, this score is identified as one of the most important predictors of disease outcome and changes from 2 to 10 (Bühmeid, 2006). It is found that using a %free PSA cut-off value of 25%, can detect prostate cancer with a 95% sensitivity and prevent 20% of unnecessary biopsies (Catalona et al., 1998). Some studies found that %free PSA may be a better predictor of postoperative pathological outcome as compared to Gleason grade (Southwick et al., 1999), although the some studies don’t confirm this opinion (Jung and et al., 2000; Graefen et al., 2002).

**Transforming Growth Factor β1 (TGFβ1)**

A prominent regulator of the normal and malignant prostate is TGFβ1. This multifunctional cytokine causes dys regulation of cell cycle, stimulates angiogenesis also increases proteases and extra cellular matrix (Wikstrom et al., 2001; Achyut and Yang, 2011). It is indicated association between high level of this cytokine in prostate cancer tissue and increased tumor grade, tumor stage (Shariat et al., 2004b), biochemical recurrence and patterns of invasion of disease such as extra capsular extension and seminal vesicle invasion (Shariat et al., 2004a; Shariat et al., 2008b), although there are some studies indicating noassociation (Perry et al., 1997; Wolff et al., 1999).

**Alpha-methylacyl-CoA Racemase (AMACR)**

This enzyme involved in β-oxidation of branched chain fatty acids and the bile acid intermediates dihydroxycholestanolic acid and trihydroxycholostanolic acid. Particularly, it is involved in conversion of (2R) α-methyl branched chain fatty acyl-CoA to their S-stereoisomers (Van Veldhoven et al., 1997; Ferdinandusse et al., 2000). AMACR strongly produced in prostate tissue (Sardana et al., 2008), and AMACR gene over expressed in prostate cancer (Jiang et al., 2004). Some researchers found that measurements of serum AMACR auto antibodies used as highly sensitive and specific diagnostic test (Sreekumar et al., 2004). Also AMACR may have a prognostic value, because reduction of this protein has been associated with increasing possibility of biochemical recurrence and unfavorable prognosis in prostate cancer (Bishoff et al., 2014). AMACR mRNA in serum and urine can be detected by reverse transcription-PCR analysis (Al-Maghrabi et al., 2012).

**Chromogranin A**

ChromograninA (CgA), a member of the granin family of neuroendocrine secretory proteins, generated by the neuroendocrine cells in the prostate is a marker of neuroendocrine differentiation (Isshiki et al., 2002). Although serum level of CgA is not specific for prostate cancer, it is associated with tumor stage and grade (Bocan et al., 2011). It has potential to detect androgen-independent disease. There is high serum level of CgA in late-stage of disease and predict poor prognosis in androgen-independent prostate cancer following endocrine therapy (Berruti et al., 2001; Khan and Ather, 2011). Also studies revealed that serum CgA combined with serum PSA, may efficiently prophecy poor prognosis following endocrine therapy (Isshiki et al., 2002). With future clinical evaluation, it is appeared that CgA may be used as a prognostic/treatment marker for prostate cancer.

**Interleukin-6(IL-6) and the other Interleukins**

IL-6, a 30 KD glycoprotein, has role in regulation of immune system, hematopoiesis, acute phase responses, cell growth and differentiation (Nakashima et al., 2000). IL-6 involved in regulation of VEGF expression and neuroendocrine differentiation in prostate (Culig et al., 2005). It is exhibited that IL-6 acts as a paracrine and autocrine growth factor for prostate cancer cells (Shariat et al., 2001). Several studies reported that high level of IL-6 and its receptor was associated with aggressive state of disease such as higher Gleason score, advanced stage, progression of metastasis, and androgen-independent prostate cancer (Kattan et al., 2003; Shariat et al., 2004a), as well as few studies indicated reduction of survival (Michalaki et al., 2004; George et al., 2005). It should be noted that addition of pretreatment TGF-β and IL-6 receptor to the nomogram increases the prediction
of biochemical recurrence (Shariat et al., 2008a). IL-
1β, TNF-α and Interferon β (IFN β) are important
inflammatory-related molecules which may impact on
biological features of prostate tumors and outcome of
patients. The studies suggested that prostatic expression
of these molecules and their signaling proteins involved
in prediction of clinical outcome (Rodriguez-Berrigüete
et al., 2013; Eiro et al., 2014).

**Insulin-like Growth Factor and Insulin-like Growth Factor Binding Proteins (IGFBPs)**

IGF-I, IGF-II, two receptors (IGFR1, IGFR2) and
binding proteins (IGFBP1-6) constitute Insulin-like
growth factor systems. IGF-I, a strong stimulator of normal
and neoplastic cell growth, has anti-apoptotic effects on
prostate epithelial cells (Djavan et al., 2001; khodadadi
E, 2013). In vivo and In vitro experiments revealed that
proliferation of androgen-dependent and androgen-
independent prostate cancer cell lines are promoted
by IGF-1 (Chan et al., 2002)(80). The main binding
protein for IGF-1 is IGF binding protein-3(IGFBP-3) that
effects on bioavailability of IGF-1 (khodadadi E, 2013).
IGFBP-3 can reduce growth stimulating effects of IGF-1
and suppress cell proliferation in several cell systems
including prostate cancer (Safarinejad et al., 2011). This
protein stimulates apoptosis via activation of caspasases
through a death receptor mechanism in MC-7 human
breast cancer cells (Kim et al., 2004). IGFBP-3 gene
involved in cellular senescence and its expression is down
regulated in human prostate cell lines (Schwarze et al.,
2002). Low IGBP-3 level is correlated with increased
risk of aggressive and metastatic prostate cancer (Mehta et al.,
2011). The circulating level of IGF-1 and IGFBP-3 may
be effect on invasion and metastasis of low grade tumors
(Chan et al., 2002).

High plasma level of IGFBP-2, major IGF binding
protein in prostate epithelial cells, associated with
prostate cancer. Also there is inverse correlation between
IGFBP-2 level and aggressive features of higher Gleason
score, extra prostatic extension and seminal vesicle
involvement (Shariat et al., 2002). It has been suggested
that preoperative assessment of serum levels ofIGFBP-2 and
IGFBP-3 possibly useful in prostate cancer prognosis
because of their association with the risk of disease
progression and facility of measurement in the blood
(Shariat et al., 2002). Of course, some studies suggested
that serum level of IGF-1, IGFBP-2 and IGFBP-3 have
no prognostic value in progression of prostate cancer (Yu
et al., 2001).

**Prostate-Stem Cell Antigen (PSCA)**

PSCA, a glycosylphosphatidyl inositol-anchored
cell surface, mainly expressed in prostate and may be
involved in stem cell functions like proliferation or signal
transduction (Tricoli et al., 2004), also in tumor genesis,
cell adhesion and prevention of apoptosis(Reiter et al.,
1998), but exact role of PSCA in prostate is not clear
(Tricoli et al., 2004). PSCA is co-amplified with c-myc,
a tumor progression factor and oncogene (Reiter et al.,
2000). Some studies showed PSCA over expression
in great number of prostate cancers (Han et al., 2004;
Zhigang and Wenlv, 2004), which is associated with higher
Gleason grade and more progressed tumor stage,
higher degree of metastasis (Hara et al., 2002). PSCA
expression preserved in androgen-independent prostate
cancer (Zhigang and Wenlv, 2004). The recently studies
suggested that under-expression of PSCA is correlated
with metastatic progression of prostate cancer and its over
expression associated with early stage of disease (Larkin
et al., 2012). However immunohistochemical method used
in analysis of PSCA in prostate tissue, RT-PCR method
can be detected PSCA RNA in peripheral blood (Hara et
al., 2002).Perhaps with further experiments, its potential
as a blood-based biomarker more be recognized and used
for prostate cancer prognosis.

**Other Biomarkers**

There are the other candidate biomarkers that
associated with prognosis involved in different cellular
process such as: cell cycle regulation and proliferation, cell
death, signal transduction, cell adhesion and angiogenesis
(Lopergolo and Zaffaroni, 2009).

**Biomarker related to cell cycle regulation**

Dysregulation of cell cycle, especially transition of
G1to S phase, occurs in all human cancers (Lopergolo
and Zaffaroni, 2009). Cyclin/Cyclin -Dependent Kinase
(CDK) complexes control progression of G1/S phase.

There are various endogenous CDK inhibitors
with different but overlapping specificities, comprising
P27kip1, P27 WAF1, and P16INK4, some cohort studies
showed that decreased expression of P27 may be an
independent adverse prognostic factor in localized prostate
cancer (PSA recurrence) (Kuczynk et al., 2001; Freedland
et al., 2003).

It is demonstrated that P21 over expression, before
and after hormone therapy, associated with advanced
prostate cancer (Buhmeid A, 2006). This over expression
was independently linked with high biochemical failure
in patients treated with neoadjuvant androgen deprivation
before salvage radiotherapy (Rigaud et al., 2004).

Ki-67, a DNA binding protein, is present in all phases
of cell cycle except resting cells. Several studies indicated
that high Ki-67 (proliferation index) associated with high
biochemical failure in localized prostate cancer (Rubio et
al., 2005; Laitinen et al., 2008), also associated with poor
outcomelike high rate of distant metastasis and reduction
of disease-specific survival (in hormone therapy or
radiotherapy in the context of the RTOG-8610 and RTOG-
9202 clinical trials (Li et al., 2004a; Pollack et al., 2004).

**Biomarkers related to apoptosis**

There are two main pathways of apoptosis: extrinsic
and intrinsic pathway. Intrinsic or mitochondrial pathway
is activated by pro-apoptotic signals and lead to the release
of Cytochrome c from mitochondria and eventually
activation of caspase-9. P53 and BCL-2 protein family are
the main regulators of this pathway. Mutations of P53 have
been associated with prostate cancer (Quinn Di, 2005).
Abnormal P53 protein may be as a predictor of disease recurrence following radical prostatectomy. It is indicated associations between this protein and aggressive features of disease like metastasis and reduction of survival. Over expression of P53 in preoperative biopsies of patients with localized prostate cancer (treated with radical prostatectomy) was associated with increased rate of biochemical failure (Oxley Jd, 2002). In addition, cohort studies reported that over expression of P53 in patients who underwent radiotherapy with or without hormone therapy in the context of RTOG-8610 trials, predicts poor outcome of high rate of distant metastasis, decreased overall survival (Grignon et al., 1997). Proliferation blockage and apoptosis induction of prostate cancer cells are considered as new treatment for this cancer (Aghaei et al., 2011).

**PTEN (phosphatase and tensin homolog)**

PTEN is an important tumor suppressor gene. The PTEN signaling pathway has major role in the survival and proliferation of prostate cancer cells, also involves in regulation of prostate adenocarcinoma angiogenesis (Fang et al., 2007). PTEN deletion is indicated in prostate cancer (Yoshimoto et al., 2007). Some studies reported that decrease or loss of PTEN expression were correlated with more advance of disease including higher Gleason grade, greater tumor, progressive pathological stage and extra prostatic extension (Koksal et al., 2004; Yoshimoto et al., 2007). Also researches indicated that PTEN deletions and decreased its expression associated with biochemical recurrence (Chaux et al., 2012) and metastasis (Lotan et al., 2011). It is suggested that PTEN loss is correlated with suppression of androgen receptor signaling, in fact represses androgen responsive genes (Mulholland et al., 2011). However other studies indicated that PTEN expression did not prophesy prostate cancer outcome when assayed separately and it did when combined with other biomarkers (Bedolla et al., 2007; Li et al., 2011). So, it is appeared that further research is needed.

**Androgen receptor**

The Androgen receptor (AR), a nuclear transcription factor, binds male sex steroids and involves in their biological effects in target cells. AR activated transcription of androgen-dependent genes, these receptors have an important function in prostate cancer (Donovan et al., 2008). One of the important therapeutic options in advanced prostate cancer is deprivation of androgens or peripheral obstruction of androgen action, but many prostate cancers become hormone refractory, develop more and eventually lead to deadly outcome (Bumeid A, 2006). Several molecular mechanisms involve in development of hormone refractory, and androgen receptors and their signaling pathway have significant role (Linja and Visakorpi, 2001). AR over expression associated with progression, recurrence, lymph node metastasis and/or hormone refractory in prostate cancer (Quinn Di, 2005). The higher AR mRNA was independently associated with increased biochemical failure (Rosner et al., 2007). It is suggested that accurate quantification of AR at the time of prostatectomy and biopsy lead to more suitable clinical management (Donovan et al., 2008).

**Biomarker related to cellular adhesion**

Cell-cell adhesion has critical role in the maintenance of tissue structure and cohesion. Cell adhesion molecules have important role in cancer invasion and metastasis (Kuniyasu H, 2000). E-cadherin, a 120 KD transmembrane glycoprotein and a member of cadherin family, involved in cell-cell recognition and adhesion. Meta analysis studies indicated that some gene polymorphisms of E-cadherin are associated with increased risk of prostate cancer (Deng et al., 2014). Reduced expression of E-cadherin in prostate cancer samples was associated with poor prognosis and aggressive transformation (Chuapong, 2004). It is noted that low level of E-cadherin is reported in localized prostate cancer, and metastatic prostate cancer showed high expression of E-cadherin (Rubin Ma, 2001). The reduction of E-cadherin and the elevation of N-cadherin (the other classic cadherins) characterizes epithelial to mesenchymal transition (EMT) which defines as “N-cadherin switching”, EMT is associated with biochemical failure and clinical recurrence in prostate cancer (Gravdal K and et al., 2007). It is demonstrated that N-cadherin switching associated with advanced Gleason score. N-cadherin possibly used as a biomarker of aggressive prostate cancer (Jaggi M, 2006), measurement of EMT markers may involve in precise prediction of biochemical outcome after prostatectomy (Behnsawy et al., 2013).

**Biomarker related to angiogenesis**

Growth and metastatic spreading of cancer is depended on neoangiogenesis. Adhesion molecules, nitric oxide, cyclooxygenases and VEGFs regulate blood vessel formation (Kollermann, 2001). VEGF, an important regulator of angiogenesis, play a major role in tumor angiogenesis (Hicklin and Ellis, 2005). There are at least four isofoms of VEGF with various functions and receptors affinities including A,B,C,D (Quinn Di, 2005). Higher expression of VEGF occurs in prostate cancer (Erkal et al., 2014), also VEGF receptor expression arises extensively in prostate carcinoma (Kollermann, 2001). The expression of VEGF-C and VEGF-R-3 increased in prostate cancer, which have role in lymph angiogenesis and lymph node metastasis (Yang et al., 2006; Di et al., 2009). Higher VEGF-R-3 expression predicts early tumor progression following radical prostatectomy (Li et al., 2004b), also higher VEGF expression associates with recurrence and survival in localized prostate cancer (Halvorsen, 2008; Vergis et al., 2008).

Some of the biomarkers involved in prostate cancer prognosis are indicated in Table 1, with details as to characteristics and detection method.

**Prognostic Biomarkers with Genomic tests**

**Genomic classifier (GC) and Decipher**

Genomic classifier (GC) that is associated with aggressive prostate cancer is evaluated with decipher test. This novel genomic test used after prostatectomy and evaluated 22 RNA biomarkers expression associated with
Table 1. Biomarkers Involved in Prostate Cancer Prognosis (after Getzenberg, 2006; Ramirez et al., 2008)

| Marker      | Description                                                                 | Function                                                                 | Purpose                                      | Method of detection                                                                 | Advantage/ Dis advantage                                                                 |
|-------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| PSA         | A glyco-protein and a member of the kallikrein-related peptidase family secreted by the epithelial cells of the prostate gland | Serine protease involved in the liquefaction of seminal fluids. | Prognosis/ Diagnosis                      | Serum immunoassays used to measure free PSA, complexed PSA, and total PSA.         | An organ specific biomarker, easy measurement/ Lack of specificity and the inability to distinguish between aggressive and indolent cancers, poor accuracy |
| Chromogranin A | Pro-hormone peptide released by neuroendocrine cells.                  | Unclear. It has calcium-binding properties                               | Prognosis                                    | Immunoassay, immunoradiometric assay, ELISA.                                        | Potential to detect androgen-independent disease, associated with tumor stage/ It is not specific for prostate cancer |
| AMACR       | Peroxisomal and mitochondrial enzyme                                        | It has key role in β-oxidation of branched chain fatty acids and the bile acid | Prognosis/ Diagnosis                       | Immunohistochemically RT-PCR Western blot analysis in urine RT-PCR in prostatic secretions Autoantibodies to AMACR in serum | Specific biomarker/ Use in some clinical centers (microfocal cancer diagnosis on biopsy specimens) |
| IL-6        | Cytokine                                                                    | hematopoiesis the immuneresponse, the acute-phase response, differentiation of B-cells | Prognosis                                    | Immunoassay                                                                         | Easily measurement/ Increase in so much inflammatory conditions                         |
| TGFβ1       | Cytokine                                                                    | Many cellular functions, including the control of cell growth, cell proliferation and differentiation apoptosis, angiogenesis | Prognosis                                    | Immunoassays                                                                       | High level of this cytokine associate with prostate cancer/ Some studies indicated any association |
| IGF-1       | A hormone similar in molecular structure to insulin                       | A strong stimulator of normal and neoplastic cell growth, anti-apoptotic   | Prognosis/ Diagnosis                       | ELISA                                                                              | Easy measurement/ Low sensitivity and specificity                                         |
| PSCA        | Glycoprotein of cell surface                                                | Cell surface marker, possibly proliferation of stem cells signal transduction | Prognosis                                    | RT-PCR                                                                            | Over expression in great number of prostate cancer which is associated with higher Gleason grade and more progressed tumor stage, degree of metastasis |
| PSA velocity (PSAv) | Sequential evaluation of PSA levels over time                                         | ------                                                                   | Prognosis                                    | By counting of times the blood increases PSA level by 0.4ng/mL                      | High specificity/ Low sensitivity and so low specificity                                  |
| Ki-67       | A DNA binding protein                                                      | A cellular marker for proliferation, involved in cell proliferation       | Prognosis                                    | RT-PCR                                                                            | Considered as one of the most important prognosis biomarkers of prostate cancer / It is not using on common |
| P53         | A tumor suppressor protein                                                  | Regulation of intrinsic or mitochondrial apoptosis pathway                | Prognosis                                    | ELISA                                                                              | 80% to 90% accuracy/The change of expression in some of the cancers                    |
aggressive prostate cancer and metastasis risk (Mohammed, 2014). Cell cycle progression, cell adhesion and migration, motility of tumor cells also immune system modulation, androgen signaling are biological processes that depicted in GC (Erho et al., 2013).

By using long term follow up (median 16.9 year) GC was assessed for clinical adverse outcome and presented enhanced risk stratification among patients after radical prostatectomy (Erho et al., 2013). Other studies confirmed these results (Karnes et al., 2013), especially combination of GC with routine risk assessment markers make possible better recognition of high risk patients after radical prostatectomy (Ross et al., 2003).

**Cell cycle progression (CCP) gene and Polaris**

Cell cycle progression (CCP) genes can be estimate by Polaris prostate cancer test that has been confirmed in several cohorts, this test can evaluate aggressiveness of prostate cancer (Bishoff et al., 2014; Crawford et al., 2014). The CCP score is introduced as a strong predictor of prostate cancer outcome, probability of relapse or progression after prostatectomy during 10 years follow up particularly when combined with clinical variables. The researchers believed that with additional studies, CCP score may have a fundamental role in determination of appropriate treatment in prostate cancer patients (Cuzick et al., 2011; Cuzick et al., 2012).

**Genomic prostate score (GPS) and Oncotype DX**

The Oncotype DX prostate cancer is a type of test that analysis the expression level of 17 genes associated with prostate cancer aggressiveness, clinical recurrence, adverse pathology, prostate cancer death. The results of test are informed as a Genomic Prostate Score (GPS) that varies from 0 to 100. The recently studies indicated that GPS can change risk stratification and predict high grade or high stage of prostate cancer at diagnosis. GPS can help to determine the appropriate treatment, surveillance or therapy, in men with newly diagnosed low risk prostate cancer (Klein et al., 2014).

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### Table 2. Age-specific Range for PSA (Zorn KC, 2014)

| Age Range (Years) | Asian Americans | African Americans | Caucasians |
|-------------------|-----------------|-------------------|------------|
| 40-49             | 0.0 - 2.0       | 0.0 - 2.0         | 0.0 - 2.5  |
| 50-59             | 0.0 - 3.0       | 0.0 - 4.0         | 0.0 - 3.5  |
| 60-69             | 0.0 - 4.0       | 0.0 - 4.5         | 0.0 - 4.5  |
| 70-79             | 0.0 - 5.0       | 0.0 - 5.5         | 0.0 - 5.5  |

Table 3. The Association of Free/Total PSA Ratio in Men with PSA Levels of 2.1-10.0 ng/ml and Probability of Prostate Cancer (Kitagawa et al., 2014)

| Free/total PSA | Probability of Prostate cancer (%) |
|---------------|-----------------------------------|
| ≥0.08         | 64.5                              |
| 0.09-0.13     | 41.2                              |
| 0.14-0.22     | 28.5                              |
| ≥0.23         | 14.3                              |
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Maryam Esfahani et al
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