A STUDY ON SURVIVIN EXPRESSION IN PROSTATE CANCER AND BENIGN PROSTATIC HYPERPLASIA; AND ITS ASSOCIATION WITH PRE-OPERATIVE SERUM PROSTATE SPECIFIC ANTIGEN AND GLEASON SCORE IN PROSTATE CANCER

By:

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CHAPTER 1

INTRODUCTION

1.0 INTRODUCTION

Men's health has been recognized as a significant health problem in the world since the late twentieth century. Prostate cancer (PCa) and benign prostatic hyperplasia (BPH) are common urologic conditions in elderly men (Miah and Catto, 2014). In Malaysia, the state of Malaysian men's health is worrisome for several years and the cancer-related death is also becoming a major health issue with an increasing incidence in colorectal, lung, laryngeal as well as prostate cancers (Tong *et al.*, 2011).

Globally, the incidence of PCa has increased dramatically in recent years, mostly due to an aging population, the practice of prostate specific antigen (PSA) screening test and subsequent prostate biopsy. Worldwide, PCa is the second most prevalent cancer diagnosis and it became the sixth leading cause of cancer mortality in men, with a global incidence of 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in men in 2008, according to the WHO GLOBOCAN database (Jemal *et al.*, 2011). Of the number, about 14% were diagnosed within Asia Pacific region (Baade *et al.*, 2013).

Specifically in Malaysia, there were a total of 502 PCa cases diagnosed in 2007 and reported to National Cancer Registry (NCR), and it became the fourth most common cancer among men. The incidence increases after 45 years old and raised abruptly after the age of 60 with the overall age-standardized incidence of 6.2 per 100,000 populations. It was highest among the Indians followed by Chinese and Malay (Omar and Tamin, 2011). A more recent audit of cancer cases treated at a

tertiary center in Malaysia in 2008 found that the PCa treated also increased from fewer than four cases treated in 2000 to 25 cases in 2007 (Othman *et al.*, 2008).

The exact causes of PCa are remains unclear (Baade *et al.*, 2013). Currently, the main diagnostic tools for PCa include digital rectal examination (DRE), serum PSA level and transrectal ultrasonography (TRUS). However the definitive diagnosis is depends on the histopathologic verification of adenocarcinoma in prostate specimens, either from biopsy cores or operative specimens (Heidenreich *et al.*, 2012). Few previous studies suggest that inhibition of apoptosis is an important element in pathogenesis of PCa and it might also occur in BPH (Krajewska *et al.*, 2003; Novara *et al.*, 2006; Rodríguez-Berriguete *et al.*, 2010; Shariat *et al.*, 2005; Tu *et al.*, 1996).

Gleason score and cancer stage at the time of diagnosis still remain the gold standards to help for prognostication of prostate cancer (Flavin *et al.*, 2011). However, there are evidences suggesting that survivin expression in cancer cells is associated with clinicopathologic variables of aggressive disease and may represent an important prognostic marker for patient outcome (Shariat *et al.*, 2004). Clinicians have limited ability to estimate survival in patients with newly diagnosed prostate cancer, and uncertainty therefore exists about optimal treatment decisions, especially for men with localized disease (Concato *et al.*, 2009).

This study will investigate the expression of survivin in PCa and BPH and its clinical significance in PCa patients.

CHAPTER 2

LITERATURE REVIEW

2.0 LITERATURE REVIEW

2.1 Prostate Gland

In order to understand prostate cancer (PCa), it is helpful to know about the prostate and nearby structures in the body. The prostate is a chestnut-shaped gland of the male reproductive system. Anatomically, it is located below the neck of urinary bladder and in front of the rectum. The size of the prostate changes with increasing age. In younger men, it is about the size of a walnut and weighs about 30 grams, but it can be much larger in older men. The main function of the prostate is to secrete a slightly alkaline fluid that forms part of the seminal fluid, a fluid that carries sperm. Just behind the prostate are glands called seminal vesicles that make most of the fluid for semen. The urethra, the tube that carries urine and semen out of the body through the penis, goes through the centre of the prostate (*Prostate Cancer Overview*, 2015).
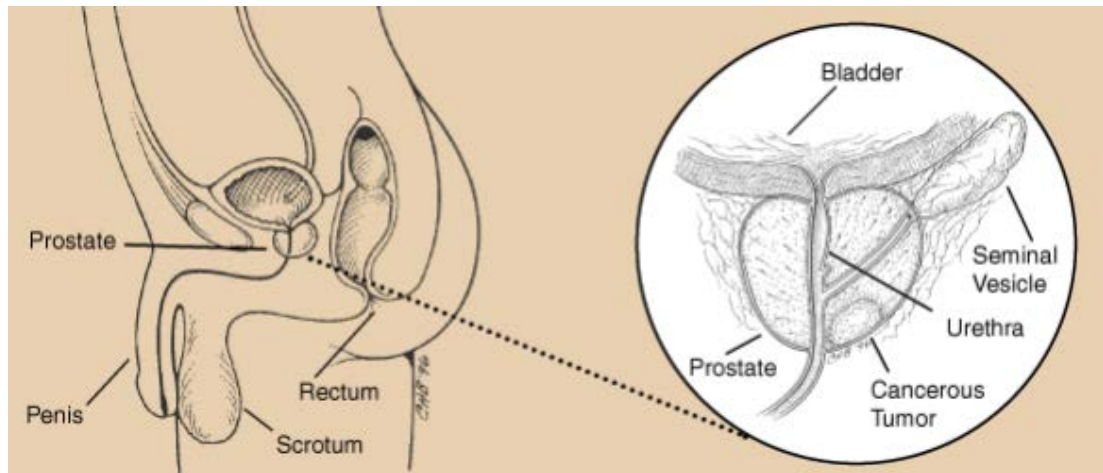
Figure 2.1: Anatomy of prostate gland. Source: *Prostate Cancer Overview*, 2015.

The prostate gland is divided into 3 zones; peripheral, transitional and central zone. The peripheral zone is the area that closest to the rectum, constitutes the largest zone of prostate gland. It can easily palpable by clinician during DRE. The majority of prostate cancer (approximately 70%) are found in the peripheral zone (Crawford, 2009), while about 25% arises in the transitional zone (Schenk *et al.*, 2011). The transitional zone is the middle area of the prostate, between peripheral and central zone. This zone makes up about 20% of the prostate gland until the age of 45 to 50 years. As men age, it may begin to undergo varying degree of enlargement stimulated by testosterone until it become the largest area of the prostate. This process called benign prostatic hyperplasia (BPH) (Medifocus.com and Jacob, 2012). Almost all BPH arises in the transitional zone (Schenk *et al.*, 2011). The central zone is the part that is farthest from the rectum. In view of this, prostate cancer that develops in this zone cannot be felt by the clinician during a DRE.
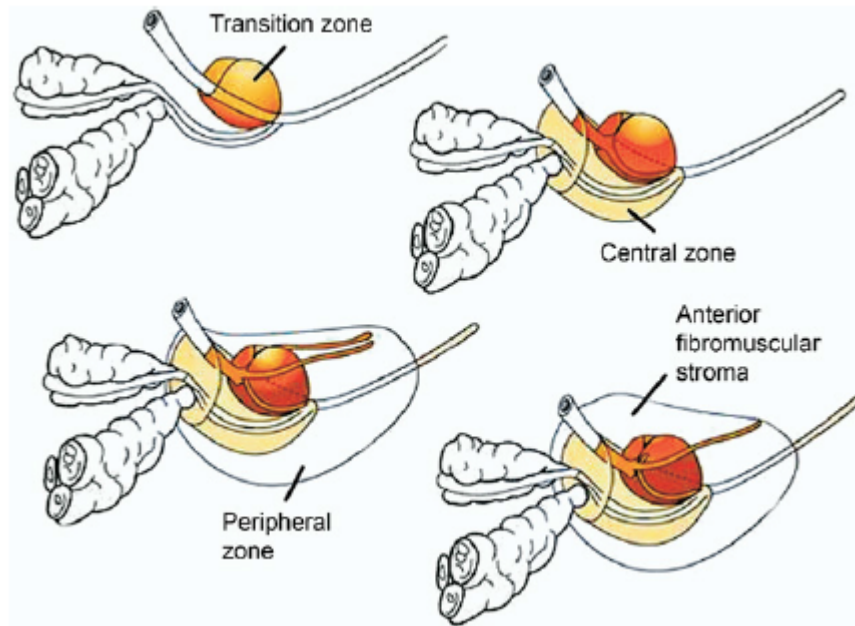
Figure 2.2: Different zones of prostate gland. Source: Crawford, 2009.

The prostate starts to develop before birth. It grows rapidly during puberty, fuelled by male hormones called androgens. The main androgen namely testosterone, is made in the testicles. The enzyme 5-alpha reductase converts testosterone into dihydrotestosterone (DHT). DHT is the main hormone that signals the prostate to grow. The prostate usually stays at about the same size or grows slowly in adults, as long as male hormones are present.

2.2: Prostate cancer

There are several types of cells that are found in the prostate, but 95% of all prostate cancers develop from the gland cells. The medical term for a cancer that starts in gland cells is adenocarcinoma. The remaining 5% of PCa cases include squamous cell carcinomas, including sarcomas, small cell carcinomas, and transitional cell carcinomas (Medifocus.com and Jacob, 2012). Thus, any PCa it is almost certain to be an adenocarcinoma.

2.2.1: Risk factors

The factors that determine the risk of developing clinical PCa are remain unclear (Baade *et al.*, 2013). However there are few well-established risk factors have been identified; increasing age, ethnicity, family history as well as saturated fat diet (Flavin *et al.*, 2011; Heidenreich *et al.*, 2011).

Most cases of PCa were diagnosed in men aged between 50 to 79 years old (Baade *et al.*, 2013). In Malaysia, the incidence of PCa (Figure 2.3) raised instantaneously after the age of 60 (Omar and Tamin, 2011). The age-standardized incidence (ASR) of PCa by ethnicity in United State was highest among black men, followed by white men; and lower among men of Hispanic and Asian/Pacific Islander (Crawford, 2009). In Malaysia, the ASR was highest among Indians (8.7 per

100,000), followed by Chinese (5.8 per 100,000) then Malay (4.9 per 100,000) (Omar and Tamin, 2011).
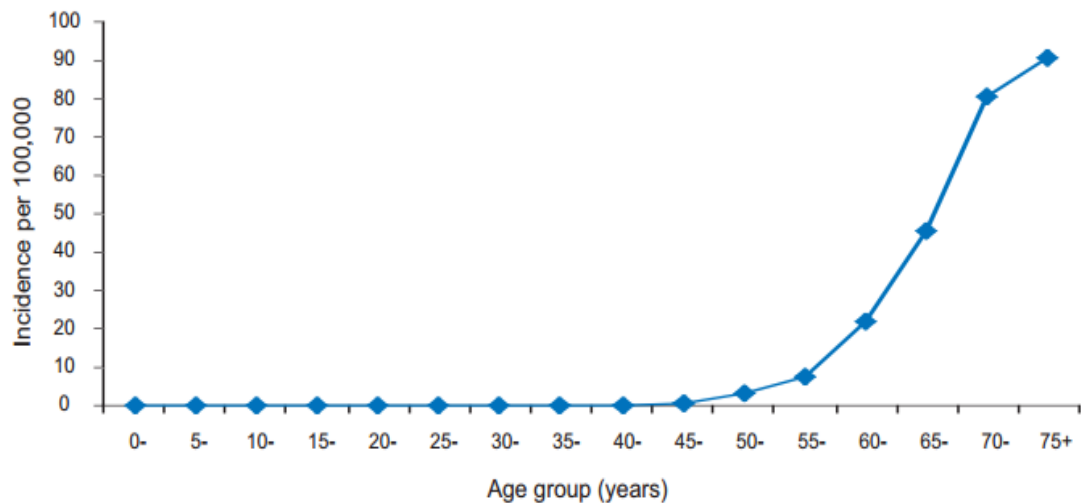

Figure 2.3: Age-specific Cancer Incidence per 100,000 population by sex, Malaysia 2007. Source: Omar and Tamin, 2011.

According to Heidenreich *et al.* (2011), if one first-line relative is affected, the risk for a man to develop PCa is at least doubled. The risk increases 5 to 11-fold, if two or more first-line relatives have the disease. However, only about 9% of individuals with PCa have true hereditary PCa. True hereditary PCa is defined as three or more relatives have PCa, or at least two who developed PCa at early onset (i.e less than 55 years old).

According to Shahar *et al.* (2011), the protective factors for PCa include high intake of fruits and vegetables, low fat diet and being physically active at middle age. Her study suggested that vegetables of specific family groups, low fat diet and

consumption of fruits; and a total serving of more than three serving per day might protect against oxidative DNA damage and subsequently decrease the risk of PCa development. A positive association of PCa risk and total fat intake was found in all ethnic groups (Whittemore *et al.*, 1995). Therefore, it is essential for Malaysian men to consume adequate fruits and vegetables, reduce fat intake and engage in physical activity in order to reduce risk of PCa (Shahar *et al.*, 2011).

Cigarette smoking is well known to cause of human malignancies such as lung cancer and has been associated with the development of many other cancers like bladder, breast, oesophagus and kidney cancer (Othman *et al.*, 2008). However, Matzkin and Soloway (1993) reviewed the literatures on the effects of cigarette smoking on PCa have found conflicting reports. The consequences of cigarette smoking on PCa are inconclusive and difficult to interpret; some studies indicate no association whereas others suggest an elevated risk among smokers (Giovannucci *et al.*, 1999). Thus, the data are not convincing that cigarette smoking results in a higher risk of PCa (Haas and Sakr, 1997).

2.2.2: Signs and symptoms

The extent of disease severity in PCa is highly variable. It may range from indolent to aggressive disease. Some men with PCa have life span similar to the general population; in contrast others develop metastatic disease that can lead to death within months (Concato *et al.*, 2009). PCa presentation is commonly asymptomatic. But once the symptoms are noticed, it usually advocates an

advanced stage of PCa (Dasgupta *et al.*, 2012). PCa commonly presents with lower urinary tract symptoms (LUTS) or prostatism symptoms such as hesitancy, nocturia, posterior dribbling, unsatisfactory voiding, incontinence, dysuria and haematuria due to blockage of the lower urinary tract by swollen prostate gland. However, symptoms of advanced PCa include dull and deep pain in the pelvic, lower back or upper thigh, weight loss, loss of appetite and fatigue.

In general, PCa is a slow-growing malignancy that needs a long development period (Rodríguez-Berriguete *et al.*, 2010). Many of them are present for years as latent neoplasms that are evident only histologically before the clinical diagnosis of PCa (Haas and Sakr, 1997). One of the reasons is that most of PCa cases (about 70%) started in the peripheral zone (Crawford, 2009).

The duration from the first histologically identifiable form of PCa until clinically evident cancer is not known, but it probably highly varies. For the small subset of all histologic cancers that discovered clinically during the lifespan of the individual, studies of tumour doubling time indicate that this process may take more than 10 to 15 years (Haas and Sakr, 1997).

2.2.3: Screening and diagnosis of prostate cancer

According to World Health Organization (WHO) guidelines, the ideal screening test for PCa is the test should be minimally invasive, easily available and easily performed, accurate, acceptable to the general population, and significantly affects outcomes of the disease, for example mortality rate (Djavan *et al.*, 2011).

European Association of Urology guideline (2015) has suggested a baseline PSA testing for men who are at risk of having PCa, which include men more than 50 years, or men aged more than 45 years with family history of PCa, or African-Americans. Men with serum PSA level >1 ng/mL at 40 years old and >2 ng/mL at 60 years old are also at higher risk of PCa metastasis or death few decades later (Mottet *et al.*, 2015). PSA testing in men older than 75 years is not recommended because its early detection would not have any clinical impact (Heidenreich *et al.*, 2012).

The main diagnostic tools for PCa include digital rectal examination (DRE), serum prostate specific antigen (PSA) level and transrectal ultrasound (TRUS); however the definitive diagnosis is depends on histopathologic verification of prostate adenocarcinoma in prostate specimens, either from biopsy cores or operative specimens (Heidenreich *et al.*, 2011).

2.2.4: Gleason score

The Gleason grading system is an important prognostic factor in PCa. The International Society of Urological Pathology (ISUP) system is clinically useful for determining the most appropriate treatments for patients with early stage PCa (Uemura *et al.*, 2009). The 2005 ISUP Modified Gleason system is the current standard for grading prostate adenocarcinoma on needle core biopsy and operative specimens. The Gleason system was introduced in1966. It has undergone series of modification and upgrading until in 2005, the ISUP had convened a conference in an attempt to achieve consensus in controversial areas regarding Gleason system. This conference yield the 2005 ISUP Modified Gleason System (Montironi *et al.*, 2010).

Gleason grading describes the degree of aggressiveness of the tumor by determining its degree of differentiation based on the appearance of the tissue under a microscope. It is an architectural grading system that ranges from well differentiated (grade 1) to poorly differentiated (grade 5) (Stark *et al.*, 2009). The Gleason score is the sum of the two highest grades assigned to two tissue areas extracted during the biopsy. The score is ranging from 2 (1+1) to 10 (5+5). A high Gleason grade (8-10) does indicate a greater chance that the cancer has spread beyond the prostate and is more aggressive type of cancer (Montironi *et al.*, 2010). In core biopsies, the worst grade should always be incorporated in the Gleason score, even if comprising < 5% of the cancer (Heidenreich *et al.*, 2012).

2.2.5: Staging

Staging is the method used by clinician to evaluate how far the cancer has spread once it has been diagnosed. It plays an important role in determining both the treatment options and predicting the prognosis. The most widely used staging system for PCa is the American Joint Committee on Cancer (AJCC) TNM system. The decision to proceed with further diagnostic or staging workup is guided by which the treatment options are available to the patient, and considering the patient's preference, age and comorbidity (Heidenreich *et al.*, 2011).

The TNM system for PCa is based on 5 key elements:

- The extent of the primary tumor (T category)

- Whether the cancer has spread to nearby lymph nodes (N category)

- The absence or presence of distant metastasis (M category)

- The PSA level at the time of diagnosis

- The Gleason score, based on the prostate biopsy (or surgery)

Based on American Cancer Society (ACS), there are 2 types of staging for prostate cancer; clinical stage and pathologic stage. The clinical stage is the clinician's best estimate of the extent of the PCa, based on the physical exam including DRE, laboratory tests, prostate biopsy, and any imaging. Whereas, the pathologic stage is based on the surgery and examination of the removed tissue. This means that after surgery, the stage of the PCa might actually change afterward. Pathologic staging is likely to be more accurate than clinical staging, as it allows the

clinician to get a first-hand impression of the extent of the disease. Both types of staging use the same categories (but the T1 category is only used for clinical staging).

Definitions

Primary Tumor (T)
CLINICAL

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically inapparent tumor neither palpable nor visible by imaging

T1a Tumor incidental histologic finding in 5% or less of tissue resected

T1b Tumor incidental histologic finding in more than 5% of tissue resected

T1c Tumor identified by needle biopsy (for example, because of elevated PSA)

T2 Tumor confined within prostate[1]

T2a Tumor involves one-half of one lobe or less

T2b Tumor involves more than one-half of one lobe but not both lobes

T2c Tumor involves both lobes

T3 Tumor extends through the prostate capsule[2]

T3a Extracapsular extension (unilateral or bilateral)

T3b Tumor invades seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall (Figure A)

Pathologic (pT)[3]

pT2 Organ confined

pT2a Unilateral, one-half of one side or less

pT2b Unilateral, involving more than one-half of side but not both sides

pT2c Bilateral disease

pT3 Extraprostatic extension

pT3a Extraprostatic extension or microscopic invasion of bladder neck[4]

pT3b Seminal vesicle invasion

pT4 Invasion of rectum, levator muscles, and/or pelvic wall

Regional Lymph Nodes (N)
CLINICAL

NX Regional lymph nodes were not assessed

N0 No regional lymph node metastasis

N1 Metastasis in regional lymph node(s)

PATHOLOGIC

pNX Regional nodes not sampled

pN0 No positive regional nodes

pN1 Metastases in regional node(s)

Distant Metastasis (M)[5]

M0 No distant metastasis

M1 Distant metastasis

M1a Nonregional lymph node(s)

M1b Bone(s)

M1c Other site(s) with or without bone disease

Figure 2.4: AJCC Prostate Cancer Staging. Source: http://www.cancer.org.

Once the T, N, and M categories have been determined, this information is combined, along with the Gleason score and serum PSA level, in a process called stage grouping. If the Gleason score or PSA results are not available, the stage can be based on the T, N, and M categories. The overall stage is expressed in Roman numerals from I (the least advanced) to IV (the most advanced). This is done to help determine treatment options and the prognosis.

ANATOMIC STAGE/PROGNOSTIC GROUPS[6]					
Group	T	N	M	PSA	Gleason
I	T1a–c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA <20	Gleason 7
	T1a–c	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason 7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA ≥20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥8
III	T3a–b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

Figure 2.5: Stage grouping, AJCC Prostate Cancer Staging. Source: http://www.cancer.org

Table 2.1: Risk groups for biochemical recurrence of localised and locally advanced prostate cancer

	Low-risk	Intermediate-risk	High-risk	
Definition	PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10-20 ng /mL or GS 7 or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			Locally advanced

Source: Mottet *et al.*, 2015.

2.2.6: Metastasis

Metastatic cancer is cancer that has spread from the place where it first started to another place in the body. It consists of series of sequential interrelated steps that lead to spread of the disease to distant organs such as bone, lymph nodes, rectum, urinary bladder, and brain, which ultimately leads to death (Dasgupta *et al.*, 2012). Hematogenous metastases were present in 35% of 1,589 patients with PCa, with most frequent involvement being bone (90%), lung (46%), liver (25%), pleura (21%), and adrenals (13 %) (Bubendorf *et al.*, 2000).

2.3: Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is a common problem among older men, which responsible for significant morbidities (Cunningham *et al.*, 2014). The prevalence of BPH rises markedly with age (Patel and Parsons, 2014). The Malaysia Ministry of Health has reported that the prevalence of BPH is about 60% in men above 60 years and rise up to 82% in men aged 71 to 80 years (Ministry of

Health, 2002). In Malaysia, the prevalence increased 8% per decade from 41.7% for men aged 50 to 59 to 65.4% for men aged 70 or more (Teh *et al.*, 2001). Many observational studies done in Europe, United State and Asia have demonstrated that older age is a risk factor for BPH onset and clinical progression (Patel and Parsons, 2014). BPH and PCa are often found concurrently, and the diagnosis of PCa is frequently made during the evaluation of obstructive symptoms associated with BPH (Haas and Sakr, 1997).

BPH is a histological diagnosis associated with unregulated proliferation of primarily stromal that composed of connective tissue and smooth muscle; and glandular epithelium within the prostate transition zone (Auffenberg *et al.*, 2009). In BPH, cellular proliferation leads to increased prostate volume and increased stromal smooth muscle tone (Patel and Parsons, 2014).

The most common presentation of BPH is the collection of symptoms described as LUTS which includes voiding symptoms (poor stream, hesitancy, terminal dribbling, and feeling of incomplete emptying) and storage symptoms (urgency, frequency and nocturia). Less frequently, BPH has been associated with other comorbidities including acute urinary retention, renal insufficiency, development of bladder calculi, urinary incontinence, and recurrent urinary tract infection (Auffenberg *et al.*, 2009).

The risk factors that has been identified are increasing age, severity of LUTS symptoms (IPSS >7), low maximum flow rate (<12 mL/s), prostate size and

significant residual urine volume (Li *et al.*, 2008). Other factors include chronic prostatitis, metabolic syndrome, obesity and genetic component to BPH (Vuichoud and Loughlin, 2015).

BPH is usually diagnosed clinically by evaluation of LUTS and DRE to assess prostate volume, prostate nodularity and asymmetry. But, DRE has low sensitivity and tends to underestimate the prostate volume (Vuichoud and Loughlin, 2015). There are two internationally validated scoring systems that can be used to assess severity of LUTS objectively; the AUA-SI (American Urological Association-Symptoms Index) and the IPSS (International Prostate Symptoms Score), which are useful in BPH management (Vuichoud and Loughlin, 2015).

2.4: Pathophysiology of prostate cancer and benign prostatic hyperplasia

Prostate cancer (PCa) and benign prostatic hyperplasia (BPH) are common urologic conditions in older men (Miah and Catto, 2014). PCa and BPH frequently coexist whereby more than 20% of PCa patients also have underlying BPH, and 10-20% of PCa is found incidentally in surgically removed BPH specimens (Schenk *et al.*, 2011).

The precise etiology for both conditions is not well understood (Baade *et al.*, 2013; Vuichoud and Loughlin, 2015). However, these two conditions have several similarities whereby the prevalence of both PCa and BPH increases with age, both

are androgen-dependent, both respond to androgen-deprivation treatments, both share similar genetic and epigenetic alterations and inflammatory components which contribute to both conditions (Schenk *et al.*, 2011).

Despite these similarities, a causal relationship between them has not been established (Miah and Catto, 2014). Differences in the anatomic location and histology of these two conditions provide the evidence that BPH does not affect PCa risk (Schenk *et al.*, 2011).

The development and progression of PCa needs a long duration, probably due to the evolution of normal prostate through phases of prostatic intraepithelial neoplasia (PIN) and possibly other atypical proliferating lesions before producing PCa (De Marzo *et al.*, 1999; Rodríguez-Berriguete *et al.*, 2010). However, development of BPH does not involve PIN, rather it is an overgrowth of both stromal and epithelial components (De Marzo *et al.*, 1999).

The correct balance between apoptosis and inhibition of apoptosis (Figure 2.6) preserves normal homeostasis and organ morphogenesis and deviations of this process can cause some human diseases such as cancer, autoimmune disease and neurodegenerative disorders (O'Driscoll *et al.*, 2003).
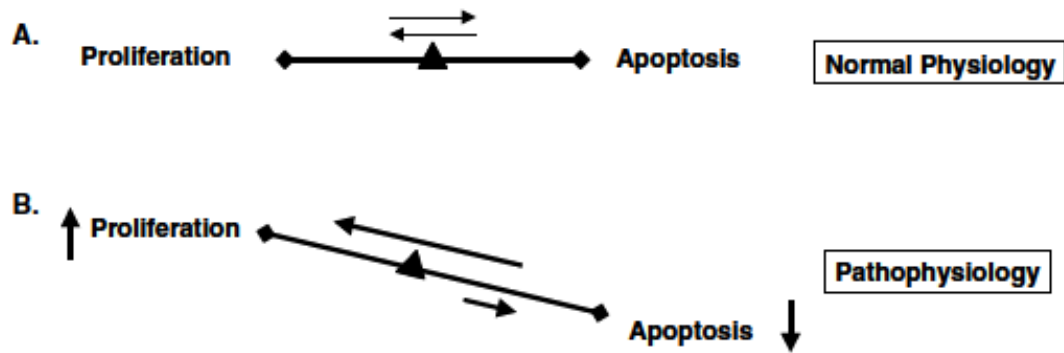
Figure 2.6: Uncontrolled cellular proliferation due to disruption of the normal balance between proliferation and apoptosis. (A) indicates normal prostate physiology when a steady state equilibrium exist between proliferation and apoptosis. (B) indicates pathophysiological conditions when the rate of cellular proliferation exceeds the rate of apoptosis. Source: Chatterjee, 2003.

In prostate carcinogenesis, few previous studies suggest that inhibition of apoptosis is a critical element that contributes to it pathogenesis, rather than enhanced cellular proliferation (Krajewska *et al.*, 2003; Tu *et al.*, 1996). Several in vitro studies also suggested that a reduction of apoptosis might occur in BPH (Novara *et al.*, 2006). Rodríguez-Berriguete *et a.* (2010) demonstrated the immunoreaction to inhibitor of apoptosis c-IAP1/2, c-IAP-2, ILP-2, NAIP, survivin, XIAP, p-Elk-1, p-ATF-2 and NF-kB in BPH tissue, which provoke the lower apoptosis index in BPH. Similar results have been reported to survivin (Shariat *et al.*, 2005).

2.5: Inhibitor of apoptosis proteins (IAPs)

IAP is a gene family that characterized by presence of baculovirus IAP repeat (BIR) domain that plays an important role in the negative regulation of apoptosis (O'Driscoll *et al.*, 2003). In human, eight members of IAPs family have been identified comprises namely Survivin, XIAP (ILP-1), c-IAP-1, c-IAP-2, NAIP, apollon (BRUCE) and ML-IAP (LIVIN) and ILP-2 (Andersen *et al.*, 2007). Among them, the most studied members of IAP gene family are XIAP, c-IAP1, c-IAP2 and Survivin (Rodríguez-Berriguete *et al.*, 2010).

Escape from apoptosis is one of the hallmarks of any tumor-initiating cell (Catalano *et al.*, 2011). Among the inhibitors of apoptosis (IAP), interest recently focused on survivin, a structurally unique, bifunctional member of the IAP protein family, which is involved in the control of mitotic progression and inhibition of apoptosis (Altieri, 2001).

2.6: Survivin

Predicting disease outcome is very important in understanding the natural history of PCa, planning treatment strategies and counselling the patient. It is also to examine and characterize tumors of poor prognosis, to predict their biology, to ensure adequate treatment and to improve patient outcome. One group of these possible factors is survivin, it inhibits apoptosis and regulates cell division and belongs to the inhibitors of apoptosis (IAP) gene family.

2.6.1: Survivin

Ambrosini *et al.* (1997) describe a new human gene encoding a structurally unique IAP apoptosis inhibitor that designated as survivin. Survivin is the smallest member of the IAP family, with a 142-amino acid, 16.5 kDa protein coded by a single-copy gene located on the human 17q25 chromosome. It plays critical role in cell division and anti-apoptosis (Mita *et al.*, 2008). Compared to other IAPs, it is structurally unique, containing a single BIR domain and long carboxyl-terminus α-helix, but there is no other identifiable protein domain (Altieri, 2010).

Survivin present during fetal development but undetectable in most terminally differentiated adult tissues other than the thymus, placenta, CD34^{+} stem cells and basal epithelial cells (Ambrosini *et al.*, 1997; Mita *et al.*, 2008). It is a striking cancer gene which is abundantly expressed in almost human cancer tissues (Altieri, 2010). Overexpression of survivin has been reported in majority of cancers including esophageal, lung, breast, colon, gastric, pancreatic, cervical, bladder, uterus, ovary as well as prostate cancer (Fukuda and Pelus, 2006). The finding of recombinant expression of survivin counteracts apoptosis of B lymphocytes precursors deprived of interleukin 3 (IL-3) suggest that apoptosis inhibition may be a general feature of neoplasia and identify survivin as a potential new target for apoptosis-based therapy in cancer and lymphoma (Ambrosini *et al.*, 1997). Before further discussion, we need to know the cell cycle and apoptotic process as survivin main functions are the regulation of cell division and the inhibition of apoptosis.

2.6.2: Cell cycle

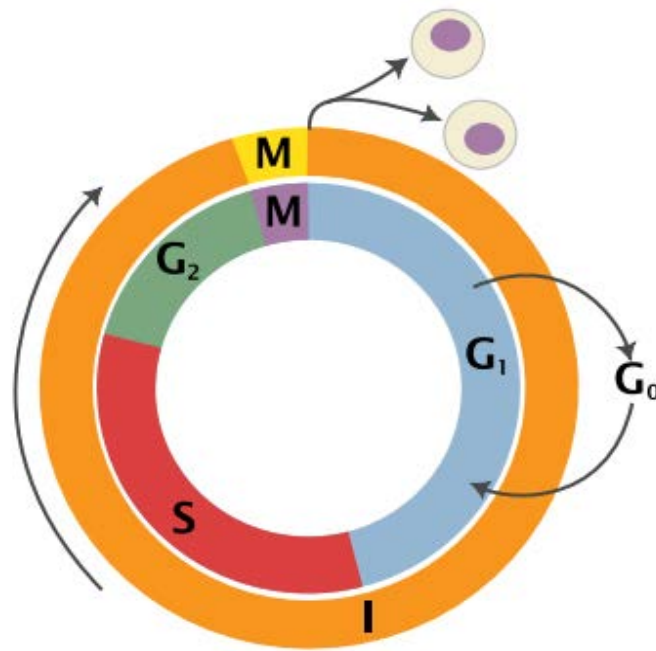Cell cycle is the sequence of events that results in cell division (Mitchell, 2015).

Figure 2.7: Phases of the cell cycle. Outer ring: I=*Interphase*, M=*Mitosis*; inner ring: M=*Mitosis*, G_1=*Gap 1*, G_2=*Gap 2*, S=*Synthesis*; not in ring: G_0=*Gap 0/Resting*. Source: (Wikipedia, 2015).

The cell cycle consists of G_1 (presynthetic growth), S (DNA synthesis), G_2 (premitotic growth) and M (mitotic) phases. G_0 is a state where the quiescent cells that do not entered the cell cycle. M phase consists of prophase, metaphase, anaphase, telophase and cytokinesis (Wikipedia, 2015). Each cell cycle phase is