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Chemopreventive Target for Prostate Cancer: Prostatic Intraepithelial Neoplasia

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1. Introduction

Prostate cancer is one of the most frequently diagnosed malignancies among the male population and the second common cancer-related death worldwide after lung cancer (Jemal *et al.*, 2010). It is estimated that 30% of male older than 50 years are harboring microscopic transformation of adenocarcinoma within the prostate gland. Because of the dramatic rise in the incidence of prostate cancer with the rate increasing approximately 6% per year worldwide (Eschenbach, 1996), the study of precursor lesions of prostate cancer is emerging concept in the field of prostate cancer prevention.

2. Prostatic intraepithelial neoplasia

John McNeal introduced the term *intraductal dysplasia of the prostate* in the early 1960s, postulating that carcinoma of the prostate arose from active ductal/acinar epithelium and not from atrophic acini (McNeal, 1965, 1988; Amin *et al.*, 1993). Later various terms have been rased such as *large acinar atypical hyperplasia with malignant change* (Allam *et al.*, 1996) and *ductacinar dysplasia* (McNeal, 1988). None of these have gained popularity. The term Prostatic intraepithelial neoplasia (PIN) was first proposed by Bostwick and Brawer in 1987, and this term was accepted at the 1989 Workshop on Prostatic Dysplasia (Bethesda, Md; March 1989) as the preferred nomenclature for this preneoplastic change (Bethesda, Md; March 1989; Drago *et al.*, 1989). PIN refers to the putative precancerous end of the continuum of cellular proliferations within the lining of prostatic ducts, ductules and acini (Bostwick and Amin, 1996; Bostwick and Qian, 2004).

PIN is the most likely precursor of prostate cancer and has been described as a premalignant or pre-invasive form of prostate cancer (Sakr *et al.*, 1993; Bostwick, 1996). Although two histopathologic lesions in the prostate were proposed as being premalignant (PIN and atypical adenomatous hyperplasia, AAH), there is less evidence of a premalignant role for AAH than there is for PIN (De La Torre *et al.*, 1993; Jones and Young, 1994; Epstein, 1994; Bostwick, 1996). Within these lesions, studies have identified impaired and abnormal

differentiation, increased proliferation, and abnormal DNA content and elevated *ras* protooncogene mRNA expression (Jones and Young, 1994). There are two grades of PIN (low-grade and high-grade), although the term PIN is usually used to indicate high-grade PIN (HGPIN). The high level of interobserver variability with low-grade PIN (LGPIN) limits its clinical utility, and many pathologists do not report this finding except in research studies. Low grade PIN (LGPIN) is only a very early precursor, and might even not be considered as a precancerous lesion. Moreover, the distinction between LGPIN and normal epithelium might be observer related (Lipski *et al.*, 1996; Zlotta and Schulman, 1999; Vis and Van der Kwast, 2001).

PIN lesions can only be diagnosed by histopathological examination of prostatic tissue. It is impossible to detect PIN clinically by digital rectal examination (DRE), prostate specific antigen (PSA) or ultrasound. Cytologically, LGPIN and HGPIN have clear and reproducible features (Table 1). Histologically, however, different architectural variations exist for HGPIN (Fig. 1). At least four distinct patterns can be distinguished: flat, tufting, micropapillary and cribriform (Bostwick, 1989). Less frequent are signet cell pattern, small cell neuroendocrine pattern, mucinous pattern and microvacuolar pattern. In the big majority of PIN-lesions, a tufting pattern can be found. Frequently, multiple patterns can be found at the same time.

Structural pattern	Low grade PIN (LGPIN)	High grade PIN (HGPIN)
Architecture	Crowding, stratification, irregular spacing	More changes, 4 patterns (T, MP, cribriform, flat)*
Nuclei	Slight enlargement, size variation	Definite enlargement, less size variation
Chromatin	Normal	Increased density and clumping
Nucleoli	Rarely prominent	Frequently prominent
Basal cell layer	Intact	May show some disruption
Basement membrane	Intact	Intact

* T indicates tufting; MP- micropapillary.

Table 1. Prostatic intraepithelial neoplasia (PIN): diagnostic criteria modified from Bostwick and Brawer (1987)

HGPIN is the most significant risk factor for prostate cancer in needle biopsy specimens. Its role as the preinvasive stage of cancer was recently confirmed conclusively in two separate mouse models (Kasper *et al.*, 1998; Garabedian *et al.*, 1998). PIN coexists with cancer in more than 85% of cases (McNeal and Bostwick, 1986; Qian *et al.*, 1997) but retains an intact or fragmented basal cell layer, unlike cancer, which lacks a basal cell layer (Bostwick and Brawer, 1987). PIN is strongly predictive of adenocarcinoma, and its identification in biopsy

specimens of the prostate warrants further search for concurrent cancer. PIN alone has no apparent influence on serum PSA concentration, and it is not apparently visible by current imaging techniques.

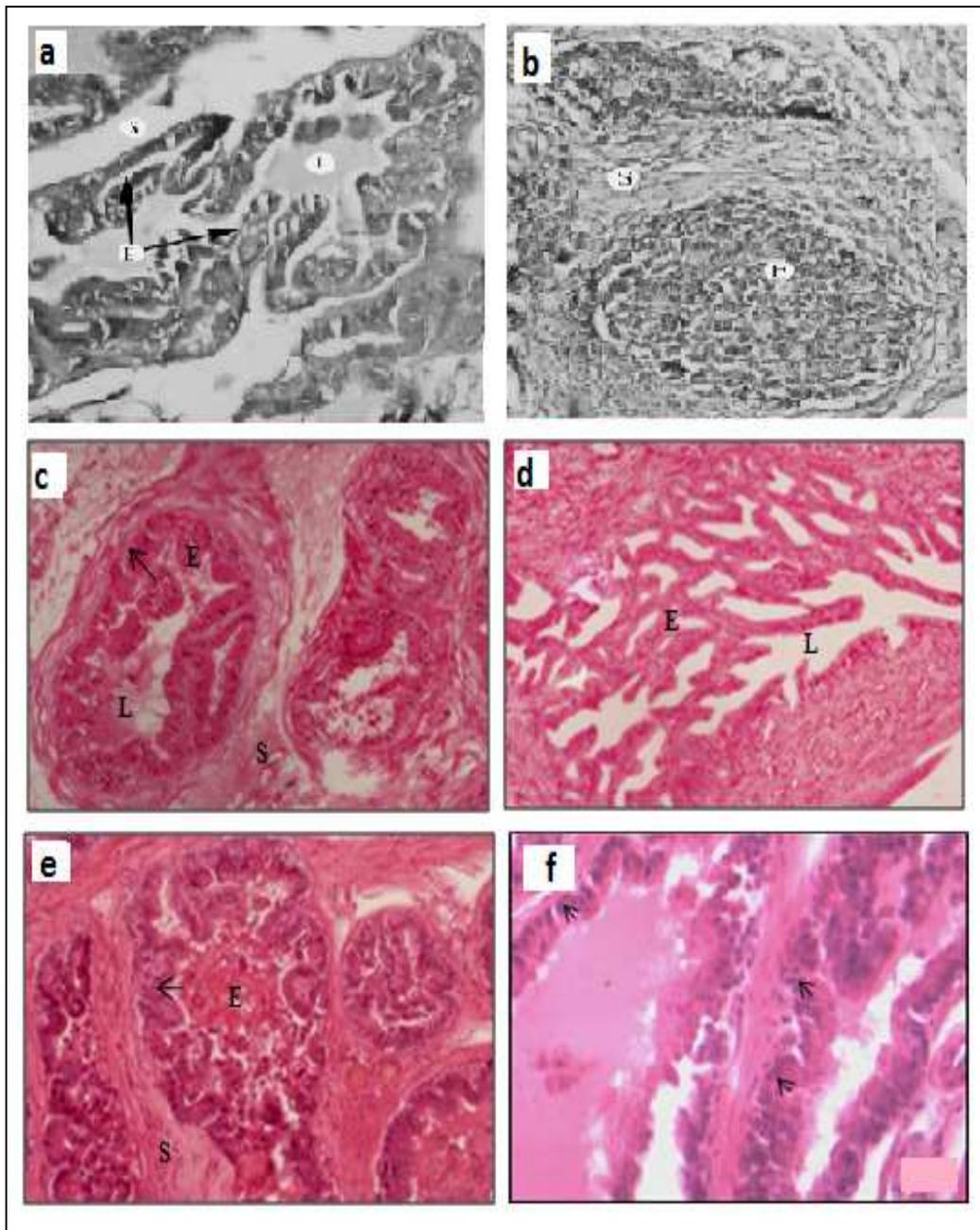


Fig. 1. Prostatic intraepithelial neoplasia Histology. (a). Multiple dysplastic and hyperplastic sites were seen within the same glandular epithelium ($\times 200$ magnifications; H&E) (b). Fully developed PIN with loss of basal epithelial cells ($\times 200$ magnifications; H&E) (Arunkumar *et al.*, 2006). Architectural pattern of high grade prostatic intraepithelial neoplasia (PIN) such as tufting (c), cribriform (d), and micropapillary (e) structures were observed ($\times 200$ magnifications; H&E) (f). The cell number in PIN was markedly increased, and cell density with sparse cytoplasm (arrow headed) ($\times 400$ magnifications; H&E) (Banudevi *et al.*, 2011a & b). E- Epithelium; L- Lumen; S-Stroma

3. Identification of PIN: Histological criteria

The classification of PIN into low grade and high grade is based mainly on the cytological characteristics of the cells. The nuclei of cells composing LGPIN are enlarged, vary in size, have normal or slightly increased chromatin content, and possess small or inconspicuous nucleoli (Figs. 2 and 3). HGPIN is characterised by cells with large nuclei of relatively uniform size, an increased chromatin content, which might be irregularly distributed, and prominent nucleoli that are similar to those of carcinoma cells (Fig. 4). The basal cell layer is intact or rarely interrupted in LGPIN, but may have frequent disruptions in high grade lesions. Although the cytological features of LGPIN and HGPIN are fairly constant, the architecture shows a spectrum, varying from a flattened epithelium to a florid cribriform proliferation. Four basic patterns that often coexist have been described by Bostwick and colleagues (Bostwick *et al.*, 1993): flat, tufting, micropapillary, and cribriform. Familiarity with this diverse architectural spectrum may facilitate the histological recognition of PIN, even though these various architectural patterns have no apparent clinicopathological relevance (Bostwic *et al.*, 1993).

Neuroendocrine differentiation occurs in PIN, where it is intermediate in degree between normal prostate (which has the most cells with neuroendocrine differentiation) and carcinoma (Bostwick *et al.*, 1994a; Di Sante Agnese, 1996). Paneth cell like change of the prostatic epithelium (neuroendocrine cells with large eosinophilic granules) is considered to be a distinct form of neuroendocrine differentiation characterised by isolated cells or small groups of cells with prominent eosinophilic cytoplasmic granules.

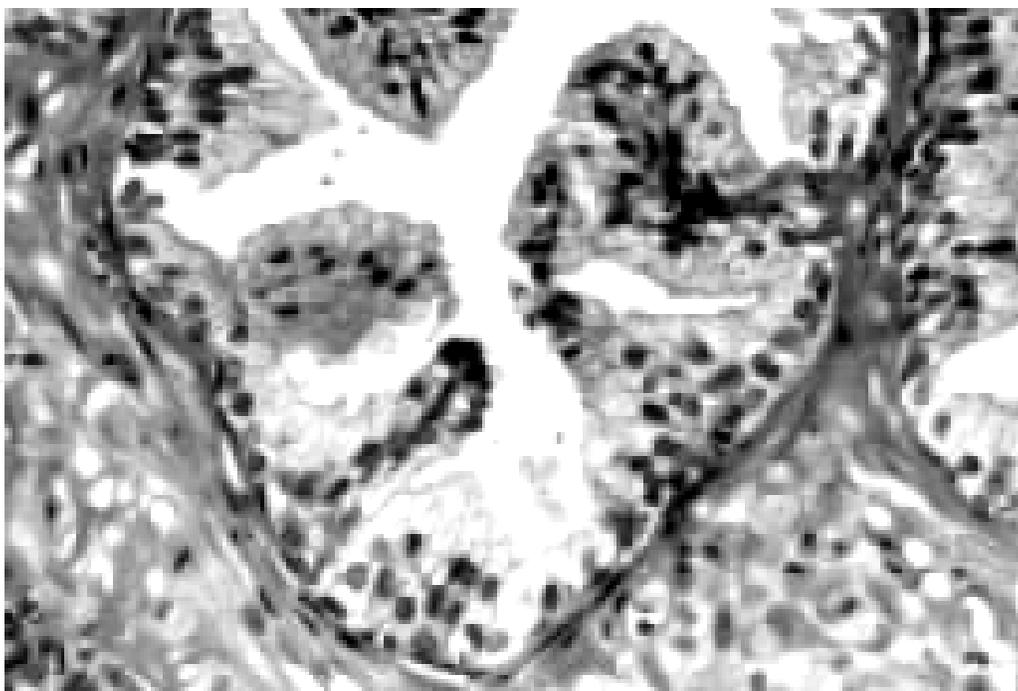


Fig. 2. **Normal prostate.** The duct is lined by a two cell layer- for example, the basal cell and the secretory or luminal cell layers.

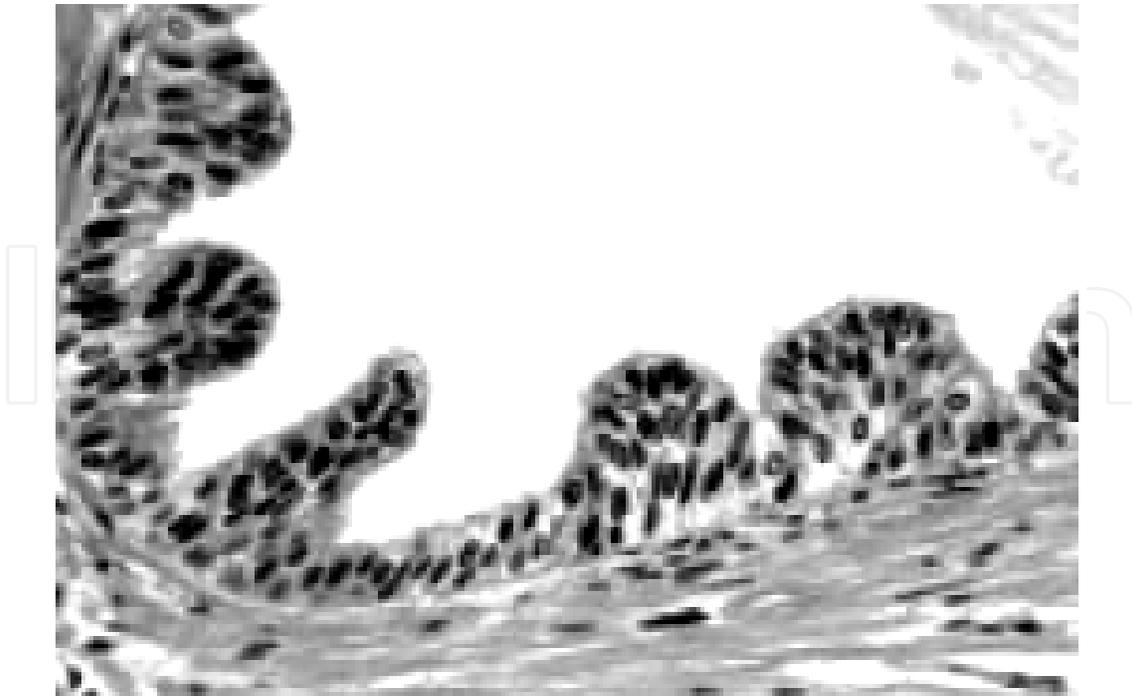


Fig. 3. Low grade prostatic intraepithelial neoplasia. The nuclei of the secretory cells are enlarged, vary in size, have normal or slightly increased chromatin content, and possess small or inconspicuous nucleoli. The basal cell layer is almost intact.

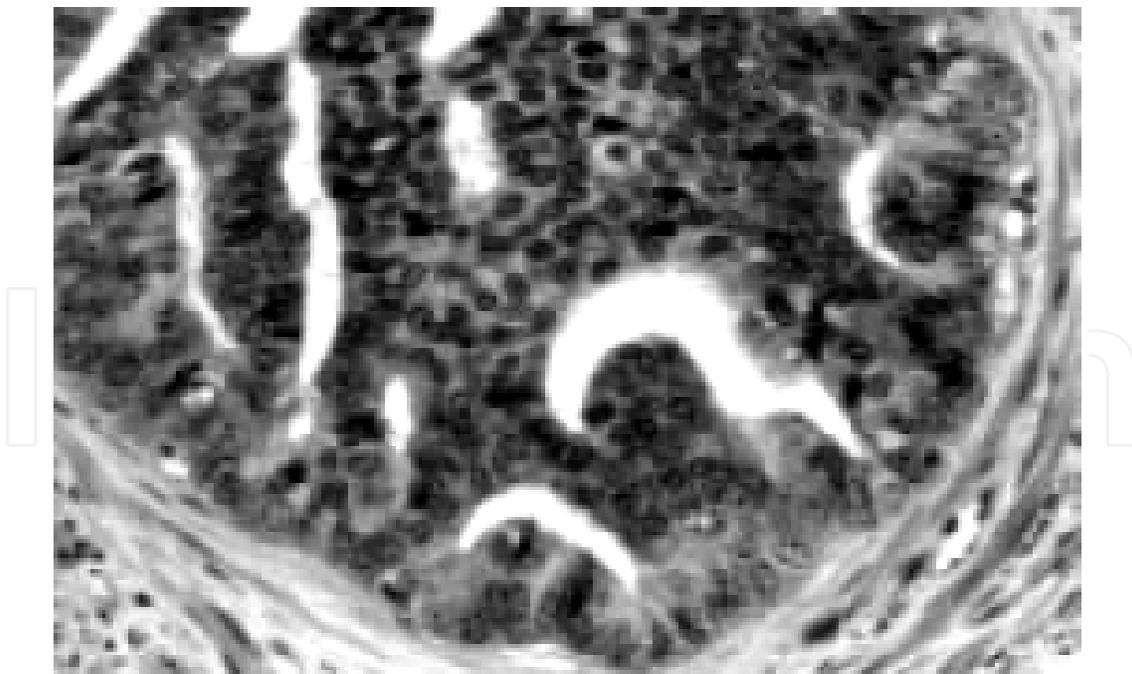


Fig. 4. **High grade prostatic intraepithelial neoplasia** with cribriform patterns. The perimeter cells show features of clearly dysplastic cells, whereas, going from the periphery towards the centre, the nuclei become smaller and the nucleoli become less apparent (“maturation phenomenon”). The basal cell layer is disrupted.

4. PIN incidence

The incidence of PIN varies according to the male population. The lowest likelihood is in men participating in PSA screening and early detection studies, with an incidence of PIN in biopsies ranging from 0.7% to 20% (Bostwick *et al.*, 1996; Langer *et al.*, 1996; Wills *et al.*, 1997; Skjorten *et al.*, 1997). Men seen by urologists in practice have PIN in 4.4% to 25% of contemporary 18-gauge needle biopsies obtained by urologists. Those undergoing transurethral resections have the highest likelihood of PIN, varying from 2.8% to 33% (Pacelli *et al.*, 1997). In such cases, all tissues should be examined, but serial sections of suspicious foci are probably not usually necessary. Select anti-keratin antibodies such as 34 β -E12 (high molecular weight keratin) may be used to stain tissue sections for the presence of basal cells, recognizing that PIN retains intact or fragmented basal cell layer, whereas cancer does not (Bostwick and Brawer, 1987). By immunohistochemical analysis, Prostate tumor overexpressed-1 (PTOV1) was considered as good marker for PIN which shows strong immunoreactivity in areas of carcinoma and HGPIN (Morote *et al.*, 2008)

5. PIN distribution

Prostatic intraepithelial neoplasia is found predominantly in the peripheral zone of the prostate (75%–80%), rarely in the transition zone (10%–15%), and extremely rarely in the central zone (< 5%). This distribution parallels the frequency of the zonal predilection for prostatic carcinoma (Bostwick *et al.*, 1995; Gaudin *et al.*, 1997; Pacelli *et al.*, 1997). The frequency of HGPIN in needle biopsy series ranges from 5% to 16% and in transurethral resection of the prostate specimens between 2.3% and 4.2% (Bostwick *et al.*, 1995; Gaudin *et al.*, 1997; Melissari *et al.*, 2006) McNeal in 1969 mentioned the multifocality of this process (McNeal, 1969; 1988); this observation has since been corroborated by others.

6. Immunohistochemistry in PIN

Numerous studies to highlight the basal cells and the secretory cells have been done (Brawer *et al.*, 1985; McNeal *et al.*, 1988a, 1988b; Perlman and Epstein, 1990; Abhrams *et al.*, 2002; Zhou *et al.*, 2003; Wu *et al.*, 2004). The basal cells and luminal cells of the prostatic glands display different keratin immunoreactivity. The high-molecular-weight cytokeratin monoclonal antibody (clone 34 β E12, also referred to as CK903) recognizes keratin proteins of 49, 51, 57, and 66 kD and labels the basal cells but not the luminal/secretory cells of the prostatic glands that stain with prostate-specific antigen and prostatic acid phosphatase. α -Methylacyl CoA-racemase (AMACR) stains the cells of adenocarcinoma but usually does not stain benign prostate glands (Brawer *et al.*, 1985; McNeal *et al.*, 1988a, 1988b; Perlman and Epstein, 1990; Abhrams *et al.*, 2002; Zhou *et al.*, 2003; Wu *et al.*, 2004).

Other antibodies that also mark basal cells include p63 (McNeal, 1969) and CK5/6 (Abhrams *et al.*, 2002). p63 is a nuclear stain, whereas CK5/6 stains the cytoplasm (Abhrams *et al.*, 2002; Zhou *et al.*, 2003). The basal cell layer is present in benign epithelial proliferations, may be disrupted in HGPIN, and is absent in invasive carcinoma (Bostwick and Brawer, 1987). Bostwick and Brawer in 1987 have shown that the frequency and extent of basal cell disruption in PIN is related to the PIN grade and is greatest in HGPIN.

A numerous of Immuno histochemical studies (McNeal *et al.*, 1988a; Perlman and Epstein, 1990; Deschenes and Weidner, 1990; Nagle *et al.*, 1991; Sesterhenn *et al.*, 1991) have been done to correlate the relationship between HGPIN and invasive carcinoma, Including evaluation of monoclonal antikeratin antibody, KA4, *Ulex europaeus* lectin (UEA-I), lectin binding pattern, and vimentin. Wu *et al.* demonstrated that a significantly higher P504S (AMACR) positive rate (56.0%) was found in isolated HGPIN glands adjacent to cancer (distance less than 5 mm) compared with those away from cancer (distance more than 5 mm; 14%, $P < 0.001$) (Wu *et al.*, 2004). High-grade PIN glands adjacent to cancer also showed a higher ($P < 0.001$) P504S intensity than did those away from cancer.

Other studies including argyrophilic nucleolar organizer regions and static DNA flow cytometry suggest that HGPIN and carcinoma have similar proliferative activity and DNA content, and hence HGPIN is the most likely precursor of cancer (Sesterhenn *et al.*, 1991; Weinberg and Weidner, 1993; Amin *et al.*, 1994). Cytogenetic abnormalities (involving 7q, 8q, 10q, 16q) and numerical chromosomal changes are noted in HGPIN and carcinoma (Emmert-Buck *et al.*, 1995; Macoska *et al.*, 1995; Qian *et al.*, 1999; Al-Maghrabi *et al.*, 2002). High-grade PIN and prostate cancer share genetic and molecular markers as well, with PIN representing an intermediate stage between benign epithelium and invasive carcinoma (Brawer, 2005).

PIN offers promise as an intermediate endpoint in studies of chemoprevention of prostatic carcinoma (Bostwick *et al.*, 1994b; Aquilina *et al.*, 1997). Recognizing the slow growth rate of prostate cancer and the considerable amount of time needed in animal and human studies for adequate follow-up, the non-invasive precursor lesion PIN is a suitable intermediate histologic marker to indicate subsequent likelihood of cancer (Aquilina *et al.*, 1997).

7. Chemoprevention strategies

Chemoprevention is the administration of agents to prevent induction of cancer, or to inhibit or delay its progression. In prostatic neoplasia, the time from tumour initiation and progression to invasive carcinoma often begins in men in the fourth and fifth decades of life and extends across decades. This phenomenon represents a unique opportunity to arrest or reverse the process of carcinogenesis with the use of chemopreventive agents. Animal models in defining efficacy of chemoprevention agents against prostate cancer. Detection of inhibitory effects on de novo prostate cancer development requires a high cancer incidence and similarity of induced tumors to human prostate carcinomas. The following animal models have produced high incidences of multifocal prostate adenocarcinoma: transgenic mice with oncogenes expressed in a prostate specific fashion; Noble rats that have been treated chronically with combination of 17 β -estradiol and testosterone; and Wistar or F344 rats treated sequentially with a single injection of *N*-methyl-*N*-nitrosourea (MNU) and chronic administration of testosterone.

PIN most often occurs in the first two models, and metastases are frequent in some transgenic models and the MNU-testosterone model (Shirai *et al.*, 1991; Pollard *et al.*, 1992; Kadomatsu *et al.*, 1993; Slayter *et al.*, 1994; Ingles *et al.*, 1997). The chemopreventive efficacy of a series of agents using a model in which hormone dependent prostate cancer is induced in the Wistar-Unilever rat (McCormick, 1998). This is achieved by sequential treatment with

an antiandrogen (cyproterone acetate), and androgen (testosterone propionate) and a direct acting chemical carcinogen (N-methyl-N-nitrosourea), followed by chronic androgen stimulation (testosterone). This regimen reproducibly induces a high incidence (< 75%) of prostate cancer, with no gross toxicity and a low incidence of neoplasia in the seminal vesicles and other non-target tissue.

Dehydroepiandrosterone (DHEA) and 9-cis-retinoic acid (9-cis-RA) are the most active chemopreventive agents identified to date. DHEA inhibits the induction of prostate cancer when administration is started before carcinogen exposure, and when it is delayed until incipient neoplastic lesions are present. Chronic administration of 9-cis-RA starting before carcinogen exposure is highly effective in the chemoprevention of prostate cancer. Liarozole fumarate confers modest protection against induction of prostate cancer, whereas N-(4-hydroxyphenyl) retinamide (4-HPR), α -difluoromethylornithine, DL- α -tocopherol acetate (vitamin E), oltipraz, and L-selenomethionine are inactive. The differential activity of 9-cis-RA and 4-HPR suggests the ligand specificity may be a determinant of retinoid action in prostate cancer chemoprevention. Chemoprevention of MNU +T induced prostate carcinogenesis at low dose level (0.5 μ g/kg body weight) of calcitriol has significant potency to inhibit prostatic hyperplasia, dysplasia and PIN, and also decreased serum PAP activity. Calcitriol may be an effective therapy for the treatment of early prostate cancer (Senthil kumar *et al.*, 2006).

Christov *et al.* (2002) studied that PIN can be used for assessing the efficacy of chemopreventive agents on prostate carcinogenesis. Diallyl disulfide, an organosulfur compound of garlic, has significant potency as an inhibitor of cancer induction in Sprague Dawley rat prostate by inhibiting PIN, hyperplastic and dysplastic foci (Arunkumar *et al.*, 2006). Zinc also acts as a chemopreventive agent against prostate cancer by inducing regression in PIN (Banudevi *et al.*, 2011a). Zinc inhibits PIN an early stage of prostate cancer. This study proves the ability of zinc to restore the PIN changes particularly in the rat ventral prostate induced by carcinogen and testosterone thereby indicating its anticarcinogenic potential (Banudevi *et al.*, 2011a). As the dorsolateral prostate is most likely homologue to the human prostate (Bosland *et al.*, 1990), in our recent study we proved that zinc was found to inhibit the growth and decrease dorsolateral prostatic acid phosphatase, zinc, citrate levels, phase I drug metabolizing enzyme activities, lipid peroxide, H₂O levels, proliferating cell nuclear antigen (PCNA), Bcl2, Bcl-X_L expressions with concomitant increase in phase II enzyme activities, GSH levels, p53, Bax, caspase-3 expressions in MNU testosterone induced model of prostate carcinogenesis (Banudevi *et al.*, 2011b). Signs of dysplasia, a characteristic of prostatic intraepithelial neoplasia, were evident in the dorsolateral prostatic histoarchitecture. Thus, zinc may act as an essential trace element against MNU and testosterone induced prostatic preneoplastic progression in Sprague Dawley rats.

The most efficient strategy for developing a chemoprevention programme is to perform two clinical trials concurrently, each based on the modulation of high grade PIN but in different target populations (Nelson *et al.*, 1996; Bostwick, 1997). In patients with high grade PIN associated with prostate cancer, a prospective, double blind, placebo controlled chemoactive pilot study designed to measure the response of a potential chemopreventive agent in the period (three to six weeks) before radical prostatectomy could easily be performed.

Androgen deprivation treatment is commonly used in this population to downsize the prostate before radical prostatectomy. This study may provide information regarding the

effectiveness of proposed agents on surrogate endpoint biomarkers, premalignant lesions, and cancer. In particular, such an investigation would determine the response of PIN to the agent in whole mounted radical prostatectomy specimens. In some preliminary investigations it has been shown that there is a marked decrease in the prevalence and extent of PIN in prostates after androgen deprivation treatment, as compared with untreated prostates (Ferguson *et al.*, 1994). This is accompanied by regressive changes in the secretory epithelium. Apoptotic bodies are more often seen in the treated normal prostate, PIN, and prostate cancer than in untreated cases. This suggests that androgen ablation induces epithelial regression by enhancing apoptosis. The low proliferating cell nuclear antigen (PCNA) and Ki67 related values and the absence of mitoses in PIN as well as in normal prostate and prostate cancer in the treated cases indicates suppressed proliferation activity as a consequence of androgen deprivation treatment (Armas *et al.*, 1993; Montironi *et al.*, 1994). It has been reported that angiogenesis is inhibited in prostate lesions when total androgen ablation induces cell regression and activation of the apoptosis (Montironi *et al.*, 1996). Consequently, the epithelial cells are blocked from expressing, producing, or exporting angiogenic molecules. All these findings indicate that the dysplastic prostatic epithelium is hormone dependent.

A short term prospective, double blind, placebo controlled phase II chemopreventive trial with cancer as an endpoint could be done in patients with high grade PIN without cancer. Chemoprevention trials designed to reverse high grade PIN may be confounded by the presence of underlying but undetected cancer addressed by requiring a second biopsy with negative findings for cancer before entry into the study (preferably sextant biopsies with special attention to areas of abnormality on ultrasonogram or digital rectal examination), and by including enough subjects in the study and control groups to equalise the risk of coexistent cancer between the two groups.

PIN is routinely monitored by repeat biopsy in contemporary urological practice. Periodic re-evaluation would be necessary, including physical examination, rebiopsy, and evaluation of surrogate intermediate endpoint biomarkers. If subsequent biopsy reveals prostate cancer, these patients need definitive treatment. Those with PIN or no malignancy need continued observation (Bostwick, 1997).

8. Clinical chemoprevention studies

Table 2 reports agents, the treatment periods, and the primary endpoints used in clinical chemoprevention studies sponsored or funded by the National Cancer Institute (Kelloff, 1997).

Green tea catechins

Epidemiological and case-control studies have garnered support for the chemopreventive properties of green tea (Jian *et al.*, 2004). A recent study was conducted on 60 volunteers with high-grade prostate intraepithelial neoplasia, a putative precursor of prostate adenocarcinoma (Bettuzzi *et al.*, 2006). Patients received green tea compounds in capsule form 200 mg three times per day. Following 1 year of treatment, only 3% of patients that received the green tea polyphenols were diagnosed with cancer compared with 30% in the placebo group. Furthermore, patients that received the green tea capsules exhibited a longer

latency to tumor detection and exhibited an improved quality of life. Another phase II study, in which 6 g/day of tea was administered to 42 patients with asymptomatic, androgen-independent prostate cancer, has demonstrated that a single patient achieved a PSA response of >50% that lasted for approximately 1 month. These patients suffered with side effects that include diarrhea, nausea and fatigue (Jatoi *et al.*, 2003). Another clinical study used 250 mg dose of green tea polyphenols twice daily. In this study, 6 out of 19 patients had disease control for 3 to 5 months and there was only 1 patient whose PSA rise was affected by green tea supplementation. The dose used in this study did not discernibly alter the course of hormone-refractory prostate cancer (Choan *et al.*, 2005). These results suggest that green tea possesses cancer chemopreventive properties and minimal anti-neoplastic activity against advance stage prostate cancer.

Agent	Cohort (treatment period)	Primary endpoints
Phase II		
DFMO	Scheduled for prostate cancer surgery (4–8 weeks)	Histopathology (PIN grade, nuclear polymorphism, nucleolar polymorphism, ploidy), proliferation biomarkers (PCNA, Ki-67)
	Scheduled for prostatectomy (stage A or B prostatic carcinoma or bladder cancer without prostatic carcinoma and scheduled for cystoprostatectomy) (14 days)	Drug effect measurements: ODC activity (skin and prostate), polyamine levels (prostate). Histopathology (TRUS guided biopsies).
	Serum PSA 3–10 ng/ml (includes patients with prostatic carcinoma and PIN) (14 days–1 year)	Biochemical biomarkers: PSA, PAP, testosterone
DHEA	Scheduled for prostate cancer surgery (28 days)	Drug effect measurements: ODC activity (skin and prostate) Polyamine levels (prostate). Histopathology (TRUS-guided biopsies) Biochemical biomarkers: PSA, PAP, testosterone
Flutamide	Patients with high grade PIN (12 months)	Histopathology (PIN grade, nuclear polymorphism, nucleolar polymorphism, ploidy). Proliferation biomarkers (PCNA, Ki-67). Genetic/regulatory biomarkers (p53, bcl-2, pc-1, chromosome 8p loss)
4-HPR	Biopsy proven non-metastatic prostate adenocarcinoma, scheduled for radical prostatectomy (4 weeks)	PIN grade and incidence, cancer incidence, nuclear polymorphism, nucleolar size, ploidy. Other endpoints: PCNA, angiogenesis, apoptosis, LOH chromosome 8; growth factors, PSA
	Scheduled for prostate cancer surgery (4–8 weeks)	Genetic/regulatory biomarkers: TGF β , c-myc, p53, plasminogen activators (tPA, uPA), apoptosis
		Histopathology: PIN grade, nuclear polymorphism, nucleolar polymorphism, ploidy. Proliferation biomarkers: PCNA, Ki-67. Differentiation biomarkers: Lewis ^x antigen. Genetic/regulatory biomarkers: p53, EGFR, TGF α
Phase III		
Finasteride	Men \geq 55 years of age with normal DRE and PSA < 3.0 ng/ml (7 years)	Prostate cancer incidence (grade and stage), BPH incidence and severity, overall and prostate-specific mortality, TURP, PSA levels
Selenised yeast	Skin cancer (melanoma, non-melanoma) patients, low Se areas in USA (~1 year)	PSA levels

BPH, benign prostatic hypertrophy; DFMO, difluoromethylornithine; DHEA, dehydroepiandrosterone; DRE, digital rectal examination; EGFR, epidermal growth factor receptor; PAP, prostatic acid phosphatase; PCNA, proliferating cell nuclear antigen; PIN, prostatic intraepithelial neoplasia; PSA, prostate specific antigen; Se, selenium; TGF, transforming growth factor; TRUS, transrectal ultrasound; TURP, transurethral resection of the prostate; 4-HPR, N-(4-hydroxyphenyl)retinamide. (Kelloff, 1997).

Table 2. National Cancer Institute Chemoprevention Branch: sponsored or funded phase II/III clinical chemoprevention trials: prostate cancer

Selective estrogen receptor modulators (SERMs)

Interest in SERMs as preventive agents has been stimulated by an apparent role of estrogens in the pathogenesis of prostate cancer, through promotion of cell growth. SERMs are generally considered to be 'weak estrogens' because they possess both agonist and antagonist activities depending on the specific tissue type and on the relative ER subtype interactions. Consequently this class of agents has been called selective estrogen receptor modulators or SERMs. As with phytoestrogens, SERMs appear to possess the ability to suppress prostate carcinogenesis. Toremifene has been evaluated in a phase IIa exploratory trial in men with high-grade PIN (Steiner and Pound, 2003). After 4 months of treatment with a daily oral dose of toremifene, 18 men with high-grade PIN underwent a repeat prostate biopsy. The prostate biopsy specimens showed significantly less high-grade PIN than historical controls. This trial provided the proof-of-concept support behind a currently open 485 patient placebo controlled, randomized dose finding phase IIb/III clinical trial

(Price *et al.*, 2006). This trial is investigating the efficacy of toremifene in reducing prostate cancer incidence in men with high-grade PIN. Men with high-grade PIN are treated for 12 months with placebo or toremifene and will undergo a repeat prostate biopsy at 6 and 12 months (the trial details are available at <http://www.gtxinc.com/tech/clinical.htm>). In addition, the National Cancer Institute is evaluating the effects of toremifene versus placebo in men with prostate cancer prior to radical prostatectomy. The objective of this phase II clinical trial is to evaluate the effects of a toremifene on biomarkers of prostate cancer. The trial details are available at <http://www.cancer.gov/search/ViewClinicalTrials>.

Difluoromethyl ornithine (DFMO)

DFMO is an irreversible inhibitor of ornithine decarboxylase involved in the synthesis of polyamines; it possesses cytostatic and cytotoxic effects (Messing *et al.*, 1999). At the clinical level, interest in exploring DFMO as a chemoprevention agent for prostate cancer has recently increased as the administration of DFMO at 0.5 g/m² daily for 4 weeks to men scheduled for surgical interventions to treat either prostatic hyperplasia or neoplasia resulted in reduction of polyamine pools, including spermine (Simoneau *et al.*, 2001). These results confirm that DFMO reaches the target tissue and hence may warrant further study as a possible chemopreventive agent for prostate cancer.

Selective COX-2 inhibitors

Inhibition of COX-2 expression blocks its pro-inflammatory effects, reduces expression of androgen receptors and androgen inducible genes and promotes apoptosis in prostate cancer cells. Selective COX-2 expression has been observed in high-grade PIN, a putative precursor of prostate cancer, suggesting a role early in carcinogenesis (Hussain *et al.*, 2003). These results support the hypothesis that inhibition of COX-2 may be an effective preventive strategy for prostate cancers; however, an industry-sponsored large-scale trial of rofecoxib was closed after the drug was withdrawn from the market because of concerns over its cardiovascular safety.

Selenium

Many of the cellular processes and molecular markers shown to be modified by selenium play key roles in prostate cancer progression. Two clinical trials are examining the role of selenium in other groups of high-risk individuals: men who have had negative prostate biopsies and men with HGPIN. The Negative Biopsy study, which includes men who have had at least one negative sextant prostate biopsy, will be using selenium supplementation in the form of selenium yeast, SeY (200 or 400 µg) (Marshall, 2001). The high-grade PIN study will determine the incidence of prostate cancer in men with biopsy-proven high grade intraepithelial neoplasia supplemented daily with 200 µg selenomethionine (Marshall, 2001). The results of these studies will be critical in defining a role for intervention with selenium in high-risk individuals, for whom there is no current treatment.

Bicalutamide

Intermittent (weekly), low-dose bicalutamide on prostate morphology revealed a tendency to a favorable modulation of high-risk proliferative lesions such as HGPIN. Namely, HGPIN status improved in 26% of treated subjects as compared with 4% of subjects in the no-treatment arm. These findings must be interpreted with extreme caution due to the inherent

limitations of prostate sampling with needle biopsy. However, our analysis including all changes in HGPIN status (i.e., both HGPIN resolution and HGPIN development after 6 months of treatment) may account, at least in part, for sampling errors, supporting the worth of our findings although they derive from a post hoc analysis. The 28% incidence of HGPIN found in our study was unusually high compared with that reported in the general population, which ranges from 0.7% to 25% in noncancerous prostate biopsies (Bubendorf *et al.*, 1998). HGPIN incidence increases with age and is higher in men seen in clinical practice compared with men participating in screening programs (Bostwick and Qian, 2004). As most subjects in our study were in their seventies and as all were urological practice outpatients, this could partly explain our findings. Moreover, whereas HGPIN by itself does not seem to increase PSA (Bostwick and Qian, 2004), the incidence of HGPIN in homogeneous cohorts of men with elevated PSA is largely unknown. Once-a-week administration of bicalutamide in men at risk for prostate cancer is feasible and reasonably safe. This finding, coupled with the encouraging signal of activity emerging from the analysis of HG-PIN changes, supports further studies of this schedule at the lowest dose for prostate cancer prevention in men at high risk despite the negative primary end-point findings on Ki-67 (Zandari *et al.*, 2009).

Nutraceuticals and Micronutrients

Nutraceutical compounds most commonly show antioxidant properties combined with other anti-neoplastic actions (Syed *et al.*, 2008). Table 3 presents the most notable nutraceutical compounds examined in prostate cancer prevention, including vitamin D, vitamin E, selenium, lycopene, soy, and green tea (Trottier *et al.*, 2010a & b).

Compound	Origin	Proposed mechanism	Strength of evidence	Outcomes	Selected references
Vitamin D (calcitriol)	Sunlight, meats, fish	Vitamin D receptor activation: cancer homeostasis, cell proliferation and differentiation	Case-control and cohort studies	Conflicting when levels are normal; modest evidence when levels are low	Trottier <i>et al.</i> , 2010 Schwartz <i>et al.</i> , 2006
Vitamin E (tocopherols and tocotrienols)	Nuts, vegetable oils, palm oil, oats, rye, wheat, rice bran	Antioxidant, proapoptotic	Cohort studies, 2 RCTs ^a	No difference from placebo in RCTs	Gaziano <i>et al.</i> , 2009 Lippman <i>et al.</i> , 2009
Lycopene	Tomatoes	Carotenoid antioxidant	Case-control and cohort studies, meta-analysis	Positive meta-analysis, but negative results from the PLCO screening trial	Etminan <i>et al.</i> , 2004 Kirsh <i>et al.</i> , 2006 Peters <i>et al.</i> , 2007
Soy and isoflavonoids	Soybeans	Phytoestrogens and tyrosine kinase inhibition causing apoptosis, limited cell growth, reduced inflammation	Case-control and cohort studies, meta-analysis	Positive effect noted with non-fermented soy and mainly in non-Western men	Yan and Spitznagel, 2009
Green tea	<i>Camellia sinensis</i> plant	EGCG is the likely active ingredient: antioxidant polyphenol and 5ARI activity	Case-control and cohort studies, 1 RCT	Conflicting for overall pCa diagnosis; possible positive effect on advanced pCa diagnosis	Kurahashi <i>et al.</i> , 2008 Brausi <i>et al.</i> , 2008

^a SELECT (Selenium and Vitamin E Cancer Prevention Trial) and Physician's Health Study II.

RCT = randomized control trial; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer; EGCG = epigallocatechin-3-gallate; 5ARI = 5 α -reductase inhibitor; pCa = prostate cancer.

Table 3. Primary prostate cancer prevention with selected nutraceutical (Trottier *et al.*, 2010)

9. Signal anomalies of human prostate cancer

Prostatic intraepithelial neoplasia (PIN) lesions could be described as low grade (LG) or high grade (HG) and it is widely perceived that HGPIN is a precursor of prostatic adenocarcinoma (Isaacs *et al.*, 2002). Since the initial growth of prostate tumor or cancer is dependent on androgens, hormone therapy in the form of medical or surgical castration constitutes a common approach for systemic treatment. However over a period of time, most cancer will develop androgen-independence, thereby making the continued androgen deprivation therapy ineffective (Taplin and Balk, 2004). While the mechanisms that drive the genesis of subclinical, microscopic PIN lesions, their progression to invasive cancer and androgen independence remain largely unknown and evidence collected in recent years point to certain molecular aberrations that pave the path of disease progression.

For example, anomalies in specific signaling molecules, including extracellular growth factors, protein tyrosine kinase cell surface receptors, intracellular transcription factors, nuclear factors and their ligands, growth suppressors, cell cycle regulators and others have indicated in some prostate carcinomas (Abate Shen and Shen, 2000; Gao and Isaacs, 2000; Roy-Burman *et al.*, 2004)

There is currently a strong focus on the genetic alterations or aberrations in gene expression that are frequently encountered in human prostate cancer in the design of mouse models. Although both men and mice harbour functionally equivalent prostate glands, there are similarities as well as differences in the anatomy and histology of the prostate in the two species. Similar epithelial cell types namely secretory, basal and neuroendocrine are found in both mouse and human prostate, although their proportions vary. While human prostate has a robust fibromuscular stroma, the mouse contains a modest stromal component. Anatomically the human prostate gland is a single, alobular structure with central, peripheral and transitional zones. In contrast, the mouse prostate is composed of four paired lobes namely anterior (AP), dorsal (DP), lateral (LP) and ventral (VP) prostate. Since DP and LP share a ductal system they are often dissected together and referred to as the dorsolateral prostate (DLP). The mouse DLP is perceived to be the most similar to the human peripheral zone in which the majority of clinically diagnosed prostate cancers are found. The mouse VP does not appear to have a human homologue and the human transitional zone does not have a murine homologue. The transitional zone constitutes a site where human nodular hyperplasia (BPH) is commonly seen. The mouse AP is analogous to the human central zone, which only infrequently represents a site of neoplasia in humans (Roy-Burman *et al.*, 2004).

10. Cell surface signaling molecules

Signaling interactions between various extracellular growth factors and the corresponding cell surface receptors converge to determine the fate of the cell with respect to proliferation, survival or death. In this context, dysregulation of several growth factors or their receptors has been implicated in prostate tumorigenesis. A number of transgenic mouse lines have been produced in which genes that are known to be overexpressed in human prostate cancer are targets. The survival factor, insulin like growth factor-I (IGF-I) which is generally overexpressed in human prostate and which may potentially be a good tumor marker in

prostate cancer was a target in a transgenic line (Woodson et al., 2003). Its expression in the mouse tissues was designed by using the bovine keratin 5 promoter (Di Giovanni et al., 2000). These mice develop squamous papillomas some of which progress to carcinomas of the skin. The increased IGF I levels also lead to pathologic changes in the prostate and in other male accessory glands of these animals (Di Giovanni et al., 2000a). The severity of the lesions in the prostate ranges from PIN to carcinoma *in situ* as well as tumors with neuroendocrine differentiation.

11. Fibroblast Growth Factors (FGFs)

The FGF family of heparin binding proteins is intercellular signaling molecules of which at least 23 different members (FGF-1 – FGF-23) have been identified to date. FGF proteins are generally secreted and their effects are mediated by a complex system of FGF receptor (FGFR) tyrosine kinases, either through autocrine or paracrine mechanisms, or both (Wilkie et al., 1995; McKeenan et al., 1998). While dysregulation of several FGFs has been described in prostate development and tumorigenesis, two members, FGF 7 and FGF 8 have been further pursued through mouse modeling experiments (Djakiew, 2000; Thomson, 2001).

FGF 8b has been demonstrated to possess the most transforming and tumorigenic potential (Daphna-Iken et al., 1998). While expression of FGF 8b appears to represent the primary species in prostatic epithelium, its expression is practically undetected in the stromal component of prostate cancer (Valve et al., 2001). Increased expression of FGF 8b in prostatic lesions beginning from PIN to adenocarcinoma and its persistence in androgen independent disease has been described. The overexpression of FGF8b in prostate cancer cells has been shown to increase proliferative and invasive properties of the affected cells directly and proliferation of prostatic stromal cells indirectly (Song et al., 2000). Consistent with these results antisense down regulation of FGF8b mRNA reduces the growth rate, inhibits cologenic activity and decreases *in vivo* tumorigenicity of prostate tumor cells (Rudra-Ganguly et al., 1998). FGF 8 expressions in prostate cancer is regulated by the androgen receptor at the transcriptional level and that FGF 8 is angiogenic further enhance the biological relevance of the factor in prostate cancer.

Prostatic hyperplasia appears in the LP and VP in some FGF 8b transgenic animals as early as 2 to 3 months and in DP and AP between 6 to 16 months. LGPIN lesions manifest from 5 to 7 months. 100% of the mice display multifocal prostatic epithelial hyperplasia during the first 14 months with 35% also having areas of LGPIN. In subsequent months (15 to 24 months) the profile changes to a higher incidence of LGPIN (66%) along with HGPIN (51%). Occasionally HGPIN lesions resemble the histopathology of human prostatic carcinoma *in situ*.

12. P27kip, regulator of cyclin-cdk activity

Activation of AKT through deregulated phosphatidylinositol 3- kinase (PI3K) signaling resulting from genetic inactivation of phosphatase and tensin homolog (PTEN), mutational activation of PI3K, or the activation of upstream oncogenic tyrosine kinases is a frequent molecular event in human cancer (Brugge et al., 2007; Lee et al., 2007). Transgenic expression

of activated AKT1 in the murine prostate induces prostatic intraepithelial neoplasia (PIN) that does not progress to invasive prostate cancer. In human epithelial cancers, reduced levels of p27^{Kip1} expression are frequently observed (Slingerland and Pagano, 2000) and are correlated with tumor progression and poor survival (Loda *et al.*, 1997; Porter *et al.*, 1997; Yang *et al.*, 1998). p27^{Kip1} functions primarily as a negative regulator of cyclin-CDK activity and thus likely participates in tumor suppression by inhibiting cell-cycle progression (Chu *et al.*, 2008). Targeted disruption of p27^{Kip1} (Cdkn1b^{-/-}) in mice leads to prostatic hyperplasia (Cordon-Cardo *et al.*, 1998) and development of pituitary adenomas (Fero *et al.*, 1996, 1998) as the mice age. However, Cdkn1b^{-/-} mice do not typically develop other spontaneous tumors (Fero *et al.*, 1996; Kiyokawa *et al.*, 1996; Nakayama *et al.*, 1996).

In many human cancer cells, oncogene-induced senescence (OIS) is associated with known tumor suppressor pathways such as p53, VHL, and Rb (Serrano *et al.*, 1997; Young *et al.*, 2008). It has been reported that OIS occurs in many human and mouse precursors of cancer and that this phenomenon can be reversed by the inactivation of tumor suppressor pathways (Braig *et al.*, 2005; Chen *et al.*, 2005; Collado *et al.*, 2005; Michaloglou *et al.*, 2005). Majumder *et al.* investigated the role of p27^{Kip1} in tumor suppression in prostate cancer using both genetically engineered mice and human prostate samples (Majumder *et al.*, 2008). They have identified a relationship among senescence induction, p27^{Kip1} expression, and PIN that supports the notion that p27^{Kip1} induction in the context of early neoplastic lesions may represent a preinvasive checkpoint linked to cellular senescence.

Importantly, this study is highly relevant to human prostate cancer (Majumder *et al.*, 2008). Indeed, we show that p27^{Kip1} is overexpressed in human PIN not associated with invasive cancer, presumably representing the earliest phase of neoplastic transformation. In contrast, PIN adjacent to invasive cancer, where checkpoint loss may have already occurred, is associated with low levels of p27^{Kip1}. The role of p27^{Kip1} in this process is further supported by a body of data showing that loss of p27^{Kip1} is commonly found in human cancers (Chu *et al.*, 2008) and that invasive tumor cells specifically degrade p27^{Kip1}. This in turn results in increased CDK2 activity (Loda *et al.*, 1997).

As many as 30% of men with a diagnosis of PIN on biopsy are subsequently found to harbor an invasive prostatic adenocarcinoma on repeat biopsy (Gokden *et al.*, 2005). Thus the CDK inhibitors might have utility in preventing cancer progression from *in situ* dysplasia to invasion.

13. Conclusions

High-grade PIN is the most likely precursor of prostatic adenocarcinoma, according to virtually all available evidence. PIN is associated with progressive abnormalities of phenotype and genotype that are intermediate between normal prostatic epithelium and cancer, indicating impairment of cell differentiation and regulatory control with advancing stages of prostatic carcinogenesis. There is progressive loss of some markers of secretory differentiation, whereas other markers show progressive increase. The clinical importance of recognizing PIN is based on its strong association with prostatic carcinoma. PIN has a high predictive value as a marker for adenocarcinoma, and its identification in biopsy specimens of the prostate warrants further search for concurrent invasive carcinoma. Studies to date

have not determined whether PIN remains stable, regresses, or progresses, although the implication is that it can progress. Chemoprevention of early stage of prostate cancer, PIN may be useful strategy in the prostate cancer prevention.

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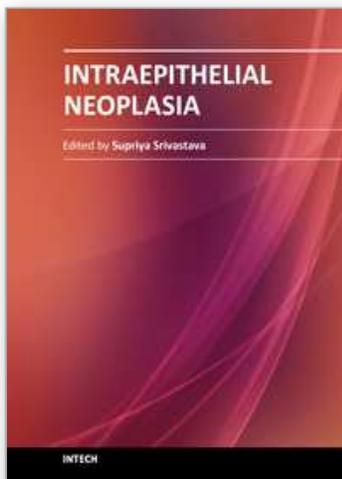
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The book "Intraepithelial neoplasia" is till date the most comprehensive book dedicated entirely to preinvasive lesions of the human body. Created and published with an aim of helping clinicians to not only diagnose but also understand the etiopathogenesis of the precursor lesions, the book also attempts to identify its molecular and genetic mechanisms. All of the chapters contain a considerable amount of new information, with an updated bibliographical list as well as the latest WHO classification of intraepithelial lesions that has been included wherever needed. The text has been updated according to the latest technical advances. This book can be described as concise, informative, logical and useful at all levels discussing thoroughly the invaluable role of molecular diagnostics and genetic mechanisms of the intraepithelial lesions. To make the materials easily digestible, the book is illustrated with colorful images.

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