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High-grade prostatic intraepithelial neoplasia

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High-grade prostatic intraepithelial neoplasia (PIN) is now accepted as the most likely preinvasive stage of adenocarcinoma, almost two decades after its first formal description. PIN has a high predictive value as a marker for adenocarcinoma, and its identification warrants repeat biopsy for concurrent or subsequent invasive carcinoma. The only method of detection is biopsy; PIN does not significantly elevate serum prostate-specific antigen (PSA) concentration or its derivatives and cannot be detected by current imaging techniques, including ultrasound. Most patients with PIN will develop carcinoma within 10 years. PIN is associated with progressive abnormalities of phenotype and genotype, which are similar to cancer rather than normal prostatic epithelium, indicating impairment of cell differentiation with advancing stages of prostatic carcinogenesis. Androgen deprivation therapy decreases the prevalence and extent of PIN, suggesting that this form of treatment may play a role in chemoprevention.
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High-grade prostatic intraepithelial neoplasia (PIN) is the earliest accepted stage in carcinogenesis, possessing most of the phenotypic, biochemical, and genetic changes of cancer without invasion of the basement membrane of the acini.[1–17] PIN is the abnormal proliferation within the prostatic ducts, ductules, and large acini of premalignant foci of cellular dysplasia and carcinoma *in situ* without stromal invasion.[18–20] The diagnostic term 'prostatic intraepithelial neoplasia' has been endorsed at multiple multidisciplinary and pathology consensus meetings,[6,14,21–24] and the interobserver agreement between pathologists has been determined to be 'good to excellent'[25,26] for high-grade PIN. Terms such as dysplasia, malignant transformation, carcinoma *in situ*, and intraductal carcinoma are discouraged.[14,27,28]

Prostatic intraepithelial neoplasia was originally graded from 1 to 3, but current recommendations recognize two grades of PIN (low grade and high grade). Grade 1 was defined as low-grade PIN, whereas grades 2 and 3 were currently considered together as high-grade PIN; currently, conventional use of the term 'PIN' without qualification refers to only high-grade PIN. High-grade PIN is a standard diagnosis that must be included as part of the reported pathologic evaluation of prostate biopsies, transurethrally resected prostate chips, and radical prostatectomy specimens. The high level of interobserver variability with low-grade PIN limits its clinical utility, and most pathologists do not report this finding except in research studies, including us.

Epidemiology of PIN

In the United States, an estimated 1 300 000 prostate biopsies are performed annually to detect 198 500 new cases of prostate cancer.[29] The incidence of isolated high-grade PIN averages 9% (range 4–16%) of prostate biopsies, representing 115 000 new cases of high-grade PIN without cancer diagnosed each year (Tables 1, 2).[29,30]

The incidence and extent of PIN appear to increase with patient age (Table 1).[31–33] An autopsy study of step-sectioned whole mount prostates from older men showed that the prevalence of PIN in prostates with cancer increased with age, predating the onset of carcinoma by more than 5 years.[33] A similar study of young men revealed that PIN is first seen in men in their 20s and 30s (9 and 22% frequency, respectively), and precedes the onset of carcinoma by more than 10 years.[33,34] Most foci of PIN in young men are low grade, with increasing frequency of high-grade PIN with advancing age. The prevalence of PIN is similar in black and white races.[33,34] The volume of high-grade PIN also increases with patient age.[31]

Race and geographical location may also influence the incidence of high-grade PIN.[5] When specific age groups are compared between races,

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there are significant differences in the frequency of high-grade PIN. For example, African-American men have a greater prevalence of high-grade PIN than Caucasians in the 50–60-year-old age group, the decade preceding the manifestation of most clinically detected prostate cancers.[21,35–37] African-American men also have the highest incidence of prostate cancer (about 50% more than Caucasians).[21,35,36,38,39] In contrast, Japanese men living in Osaka, Japan, have a significantly lower incidence of high-grade PIN compared to men residing in the United States, and Asians have the lowest clinically detected rate of prostate cancer.[40,41] Interestingly, Japanese men diagnosed with high-grade PIN also had an increased likelihood of developing prostate cancer, suggesting that high-grade PIN is a precursor of clinical prostate cancer in Asian men too.[42] Thus, the differences in the frequency of high-grade PIN in the 50–60-year-old age group across races essentially mirror the rates of clinical prostate cancer observed in the 60–70-year-old age group.[35,40]

The causal association of high-grade PIN with prostatic adenocarcinoma is based on the fact that the prevalence of both high-grade PIN and prostate cancer increases with patient age and that high-grade PIN precedes the onset of prostate cancer by less than one decade (Table 1).[33,35,36,43] The severity and frequency of high-grade PIN in prostates with cancer is greatly increased (73% of 731 specimens) when compared to prostates without cancer (32% of 876 specimens).[31,44–46] When high-grade PIN is found on sextant needle biopsy, there is a 50% risk of finding carcinoma on subsequent biopsies over 3 years,[23] although this risk is lower when more than six cores are obtained. There is also evidence to suggest that high-grade PIN may represent a precursor to a more aggressive form of prostate cancer phenotype than to those who are more likely to remain indolent.[10,42,47]

Incidence of PIN

The incidence of PIN varies according to the population of men under study (Table 2).[48–54] The lowest likelihood is in men participating in PSA

Table 1 Estimated frequency of men harboring high-grade PIN in the United States

Age (years)	*High-grade % PIN*	*US population[a] (thousands)*	*Number of PIN*
40–49	15.2	20 550	3 123 600
50–59	24.0	14 187	3 404 880
60–69	47.3	9 312	4 404 576
70–79	58.4	6 926	4 044 784
80–89	70.0	2 664	1 864 800
	Total	53 639 000	16 842 640

[a]1990 US census.

Table 2 Incidence of isolated high-grade PIN in prostatic needle biopsies

Reference	*Patient population*	*No. of men*	*Incidence of PIN (%)*
Screening programs			
Mettlin *et al* (1991)[178]	American Cancer Society National Prostate Cancer Detection Project	330	5.2
Richie *et al* (1994)[48]	Screening population	163	8.6
Feneley *et al* (1997)[179]	Screening population in Gwent, England, 1991–1993	212	20
Hoedemaeker *et al* (1999)[50]	PSA screening study in Rotterdam (Netherlands)	1824	0.7
Urology practice			
Lee *et al* (1989)[32]	Consecutive biopsies of hypoechoic lesions at St. Joseph Mercy Hospital	256	11
Bostwick *et al* (1995)[180]	Consecutive biopsies at Mayo Clinic	200	16.5
Bostwick *et al* (1995)[180]	Consecutive biopsies at Glendale Hospital (CA)	200	10.5
Langer *et al* (1996)[51]	Consecutive biopsies at University of Pennsylvania Med. Ctr.	1275	4.4
Wills *et al* (1997)[52]	Consecutive biopsies at Johns Hopkins Hospital	439	5.5
Skjorten *et al* (1997)[53]	Consecutive biopsies from 1974–1975 at Ullevaal and Lovisenberg Hospitals, Oslo, Norway	79	7.6
Perachino *et al* (1997)[54]	Consecutive biopsies	148	14.1
Feneley *et al* (1997)[49]	Consecutive biopsies at University College London Hospitals 1988–1994	1205	11
Feneley *et al* (1997)[49]	Consecutive biopsies of symptomatic men at St. Bartholomew's Hospital, London, 1993–1994	118	25

screening and early detection studies, with an incidence of PIN in biopsies ranging from 0.7 to 20%.[48–54]

Men seen by urologists in practice have PIN in 4.4–25% of contemporary needle biopsies. Those undergoing transurethral resection have the highest likelihood of PIN, varying from 2.8 to 33% (Table 3).[53,55,56] In such cases, all tissue should be examined, but serial sections of suspicious foci are usually not necessary. Unfortunately, needle biopsy specimens fail to show the suspicious focus on deeper levels in about half of cases, precluding assessment by immunohistochemistry and compounding the diagnostic dilemma.

Diagnostic criteria of PIN

There are four main patterns of high-grade PIN: tufting, micropapillary, cribiform, and flat (Figures 1–4).[57] The tufting pattern is the most common, present in 97% of cases, although most cases have multiple patterns. There are no known clinically important differences between the architectural patterns of high-grade PIN, and their recognition appears to be only of diagnostic utility. Nonetheless, one report suggested that the cribriform pattern may indicate higher risk of coexistent cancer, but this has been refuted. Other unusual patterns of PIN include the signet ring cell pattern,

Table 3 Incidence of isolated high-grade pin in prostatic transurethral resections

Reference	*Specimen*	*Patient population*	*Number of men*	*Incidence of PIN (%)*
Gaudin *et al* (1997)[55]	TURP	Consecutive TURPs without cancer at Johns Hopkins Hospital	158	3.2
Pacelli and Bostwick (1997)[159]	TURP	Consecutive TURPs without cancer at Mayo Clinic	570	2.8
Skjorten *et al* (1997)[53]	TURP	Consecutive TURPs from 1974–1975 at Ullevaal and Lovisenberg Hospitals, Oslo, Norway	731	33

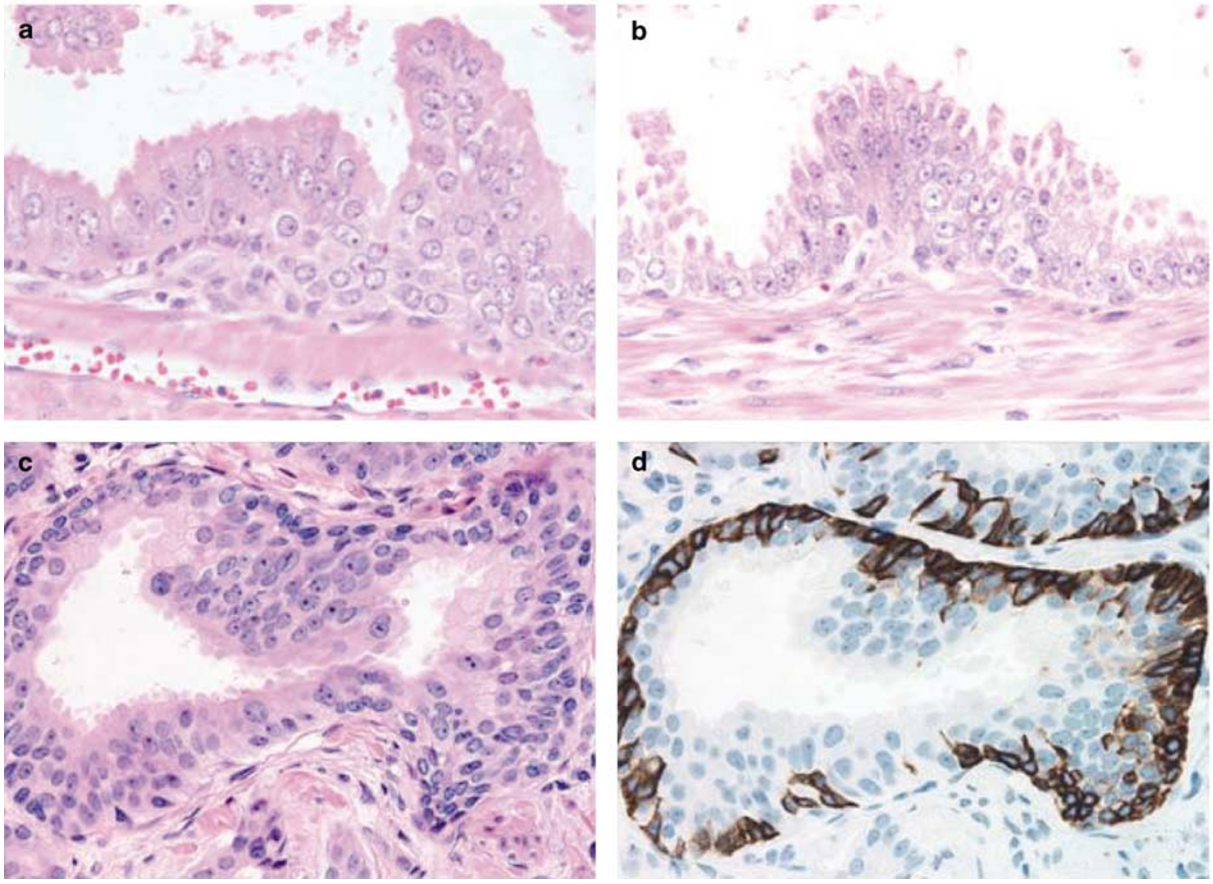

Figure 1 High-grade PIN, tufting pattern. (**a**) (**b**) and (**c**) Epithelial cell crowding and stratification with prominent nuclei and nucleoli; (**d**) immunostain for basal cell-specific high molecular weight keratin (34βE12) reveals basal cell layer disruption in high-grade PIN.

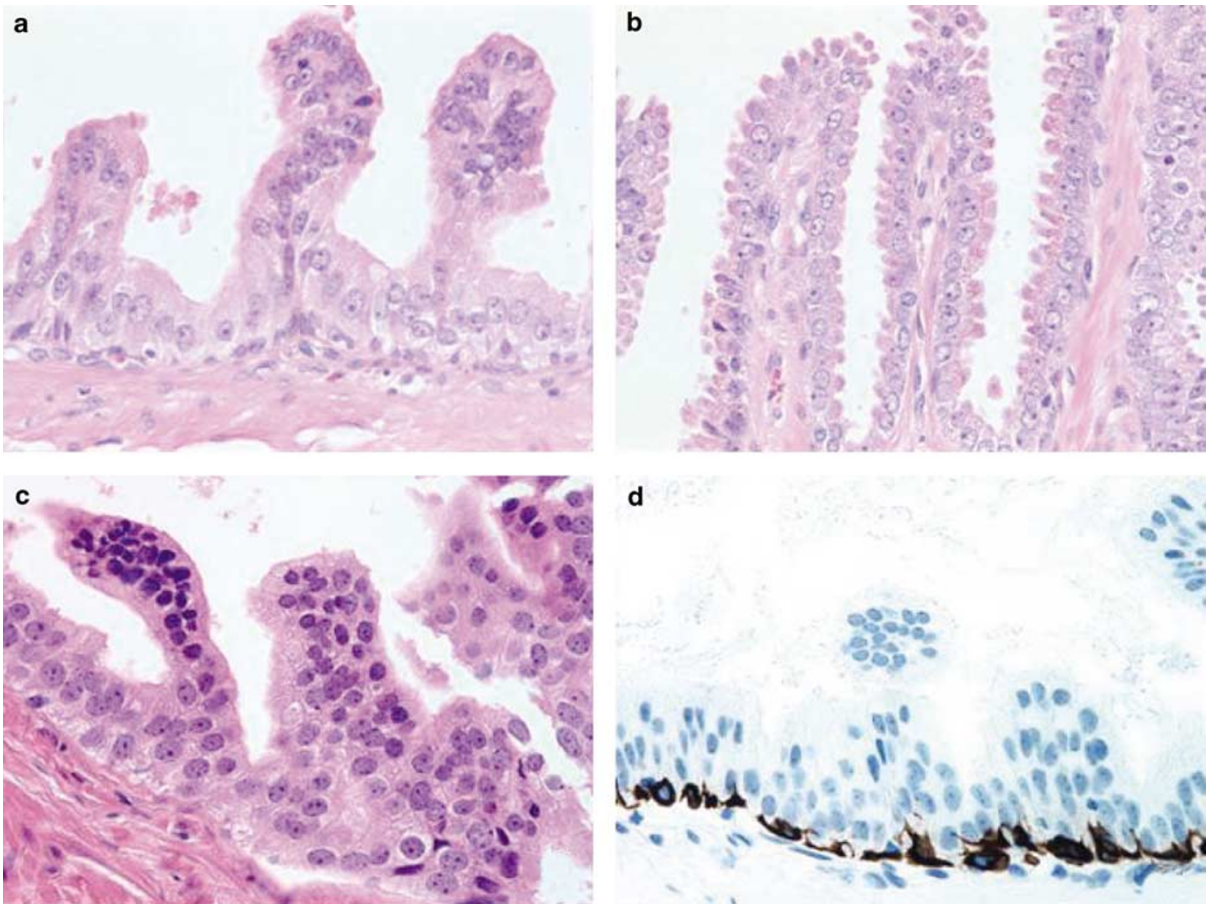

Figure 2 High-grade PIN, micropapillary pattern.

small-cell neuroendocrine pattern, and foamy gland pattern (Figures 5–8).[58]

There is inversion of the normal orientation of epithelial proliferation with PIN; most proliferation normally occurs in the basal cell compartment, whereas in PIN, the greatest proliferation occurs on the luminal surface, similar to preinvasive lesions in the colon (tubular adenoma) and other sites.

PIN spreads through prostatic ducts in multiple different patterns, similar to prostatic carcinoma. In the first pattern, neoplastic cells replace the normal luminal secretory epithelium, with preservation of the basal cell layer and basement membrane. This pattern often has a cribriform or near-solid appearance. Foci of high-grade PIN are usually indistinguishable from intraductal/intra-acinar spread of carcinoma by routine light microscopy.[59] In the second pattern, there is direct invasion through the ductal or acinar wall, with disruption of the basement membrane and basal cell layer. In the third pattern, neoplastic cells invaginate between the basal cell layer and columnar secretory cell layer ('pagetoid spread'), a very rare finding.

Early stromal invasion, the earliest evidence of carcinoma, occurs at sites of acinar outpouching and basal cell disruption in acini with high-grade PIN. Such microinvasion is present in about 2% of high-power microscopic fields of PIN, and is seen with equal frequency with all architectural patterns.[57]

The mean volume of PIN in prostates with cancer is 1.2–1.32 cm^3, and the volume increases with increasing pathologic stage, Gleason grade, positive surgical margins, and perineural invasion.[31,60] These findings underscore the close spatial and biologic relationship of PIN and cancer, and may result from an increase in PIN with increasing cancer volume. PIN and cancer are usually multicentric.[31,57,11] PIN is multicentric in 72% of radical prostatectomies with cancer, including 63% of those involving the nontransition zone and 7% of those involving the transition zone; 2% of cases have concomitant single foci in all zones.[31] The peripheral zone of the prostate, the area in which the majority of prostatic carcinomas occur (70%), is also the most common location for PIN.[31–57] Cancer and PIN are frequently multicentric in the peripheral zone, indicating a 'field' effect similar to the multicentricity of urothelial carcinoma of the bladder.

High-grade PIN and prostate cancer are morphometrically and phenotypically similar. High-grade PIN occurs primarily in the peripheral zone and is seen in areas that are in continuity with prostate cancer.[6,31,37,46,61,62] High-grade PIN and prostate

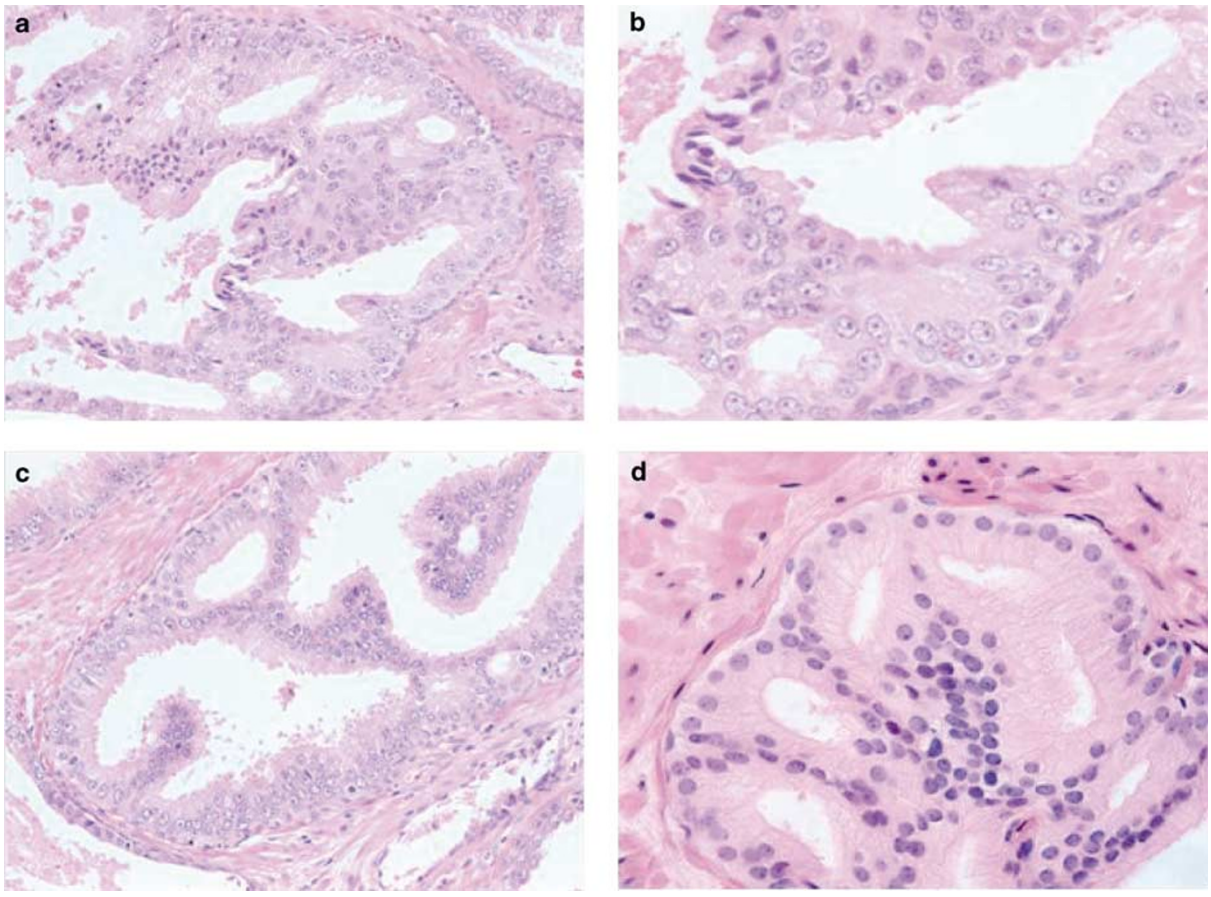

Figure 3 High-grade PIN, cribriform pattern.

cancer are multifocal and heterogeneous.[31,63,64] Increasing rates of aneuploidy and angiogenesis as the grade of PIN progresses are further evidence that high-grade PIN is a precancer.[1,62,65–68] Prostate cancer and high-grade PIN also have similar proliferative and apoptotic indices.[1,3,40,69–74]

It is often difficult with small foci in needle biopsies to separate cancer from suspicious foci (atypical small acinar proliferation suspicious for but not diagnostic of malignancy) when there is coexistent high-grade PIN; the difficulty is based on the inability to separate tangential cutting of the larger pre-existing acini of PIN (that may appear as small separate adjacent acini) from the smaller discrete acini of cancer.

Recent renewed efforts to introduce the term 'intraductal carcinoma' rely on the abandoned concept that dysplasia (defined here as malignancy arising at that specific site within the epithelium) can be separated reliably from intraductal/intracinar spread of cancer (defined here as extension of malignant cells through the pre-existing lumens of the prostate); however, this concept was rejected by consensus on multiple occasions owing to lack of reproducible criteria for making this distinction, and the noncommittal term intraepithelial neoplasia was internationally adopted and repeatedly reconfirmed as it begs the question of site of origin of the process. Those who persist with the belief that 'intraductal carcinoma' can be diagnosed rely on proximity of the epithelial abnormality to invasive cancer, but this criterion is arbitrary and not based on valid objective confirmatory data. More importantly, there is no clinical utility at present that requires separation of dysplasia and intraductal/ intra-acinar spread of cancer—the clinical response is the same. It is conceivable that future studies may allow diagnostic separation of dysplasia and intraductal/ intra-acinar spread of cancer; if so, then these steps in the biologic progression of prostate cancer may be shown to have differential predictive value for prostate cancer. We agree that identification of subsets of high-grade PIN that indicate greater risk of cancer is a clinically important area of investigation.

Immunohistochemistry of PIN

Select antibodies such as anti-keratin 34β-E12 (high molecular weight keratin) or p63 may be used to stain tissue sections for the presence of basal cells, recognizing that PIN retains an intact or fragmented basal cell layer whereas cancer does not.

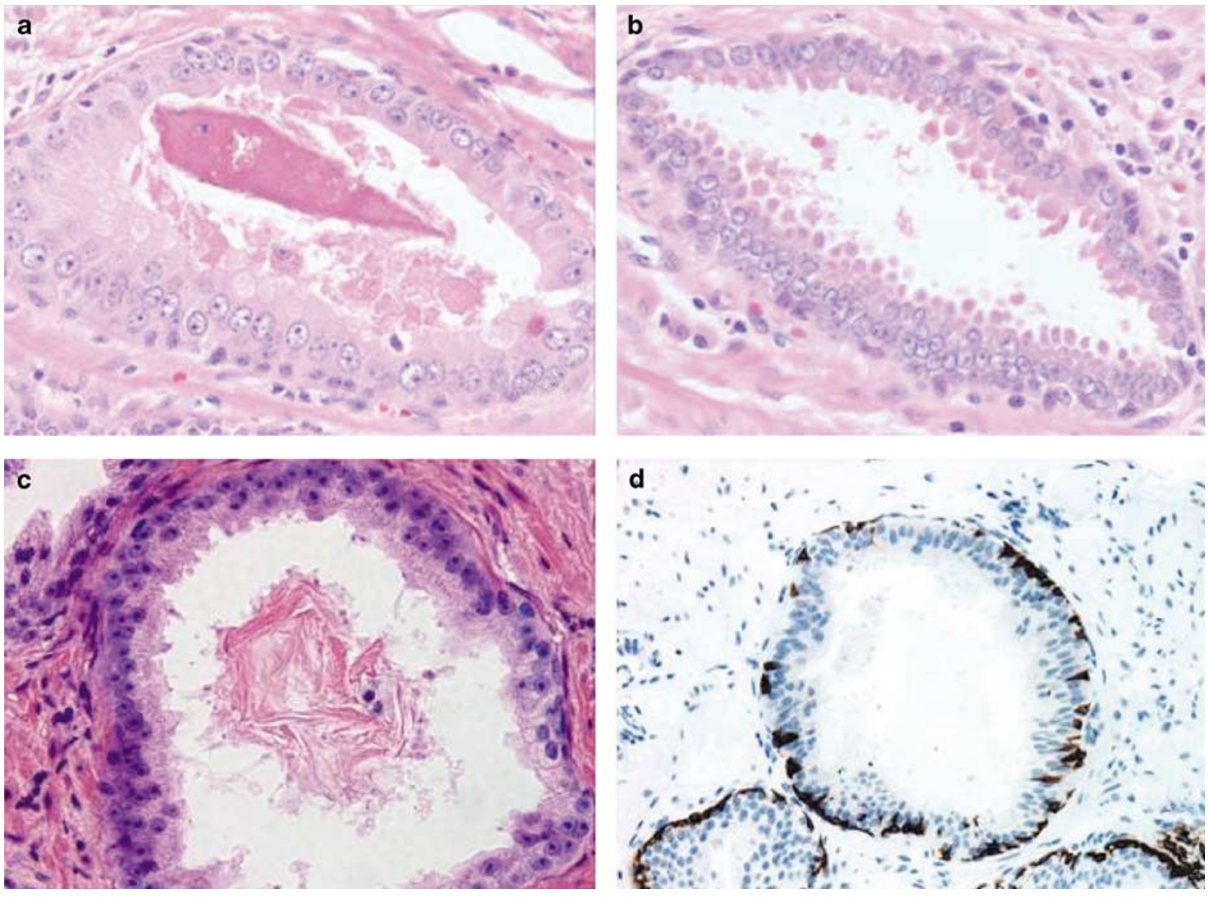

Figure 4 High-grade PIN, flat pattern.

Monoclonal basal cell-specific antikeratin 34β-E12 stains virtually all of the normal basal cells of the prostate, with continuous intact circumferential staining in many instances. There is no staining in the secretory and stromal cells. This marker is the most commonly used immunostain for prostatic basal cells,[75–77] and methods of use with paraffin-embedded sections have recently been optimized.[78] Keratin 34β-E12 is formalin sensitive and requires pretreatment by enzymes or heat if formalin-based fixatives are used. After pepsin predigestion or microwaving, there is progressive loss of immunoreactivity from one week or longer of formalin fixation. Heat-induced epitope retrieval with a hot plate yielded consistent results with no decrease in immunoreactivity with as long as 1 month of formalin fixation.[78] The staining intensity was consistently stronger at all periods of formalin fixation when the hot plate method was used, compared with pepsin predigestion or microwaving. Weak immunoreactivity was rarely observed in cancer cells after hot plate treatment, but not with pepsin predigestion or microwave antigen retrieval. Our laboratory reported that steam-EDTA in combination with protease significantly enhanced basal cell immunoreactivity compared with protease treatment alone in noncancerous prostatic epithelium (Figures 1d, 2d, 4d and 5d).[79] Nonreactive benign acini were always the most peripheral acini in a lobule, a small cluster of outpouched acini furthest from a large duct, or the terminal end of a large duct.[80] More proximal acini had a discontinuous pattern of immunoreactivity. Electron microscopy showed occasional acini with luminal cells abutting the basement membrane, without the interposition of basal cell cytoplasm, and other acini with extremely attenuated basal cell cytoplasmic processes containing sparse bundles of intermediate filaments.

Increasing grades of PIN are associated with progressive disruption of the basal cell layer, according to studies utilizing antikeratin 34β-E12. Basal cell layer disruption is present in 56% of cases of high-grade PIN, and is more frequent in acini adjacent to invasive carcinoma than in distant acini (Figures 1d, 2d, 4d and 5d). The amount of disruption increases with increasing grades of PIN. Early invasive carcinoma occurs at sites of glandular outpouching and basal cell discontinuity in association with PIN.[20] The cribriform pattern of PIN may be mistaken for cribriform adenocarcinoma, and the use of antikeratin staining is invaluable in making this distinction.[81]

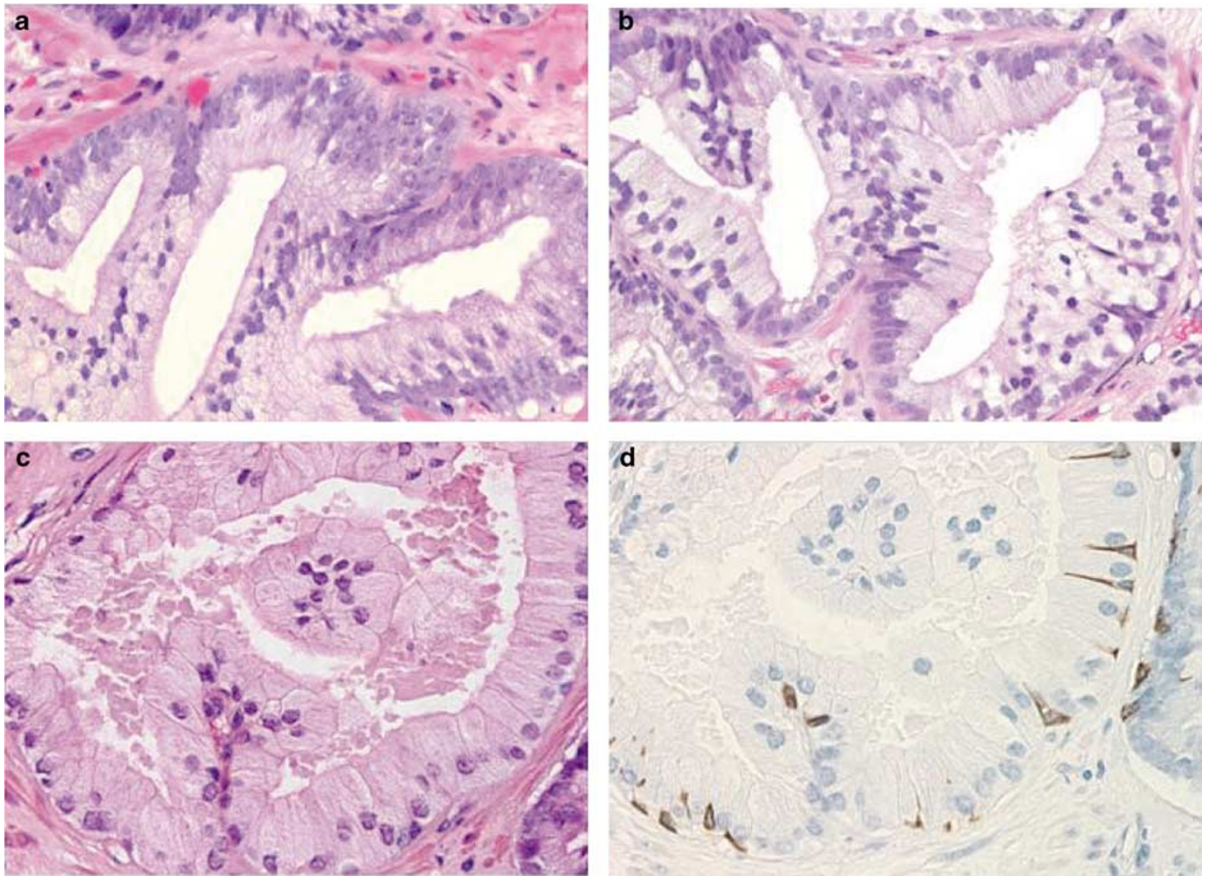

Figure 5 High-grade PIN with foamy cytoplasm (**a–c**). (**d**) Immunostain for 34β12 reveals basal cell layer disruption in high-grade PIN.

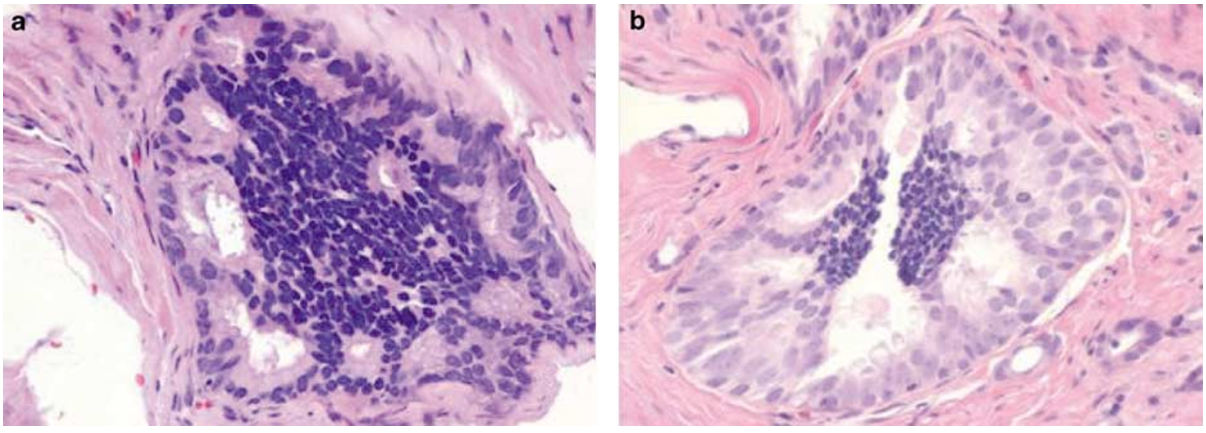

Figure 6 High-grade PIN with intraluminal small cells.

Cancer cells consistently fail to react with this antibody, although admixed benign acini may be misinterpreted as cancerous staining. Thus, immunohistochemical stains stains for antikeratin 34β-E12 may show the presence or absence of basal cells in a small focus of atypical glands, helping to establish a benign or malignant diagnosis respectively. We believe that this antibody can be employed successfully if one judiciously interprets the results in combination with the light microscopic findings; relying solely on the *absence* of immunoreactivity (absence of basal cell staining) to render the diagnosis of cancer is without precedent in diagnostic immunohistochemistry and is discouraged.[82] Nonetheless, recent reports have noted that the rate of equivocal cases can be reduced considerably,[83] by 68%,[75] or from 5.1 to 1.0 %[84] by addition of this immunohistochemical marker. Evaluation of

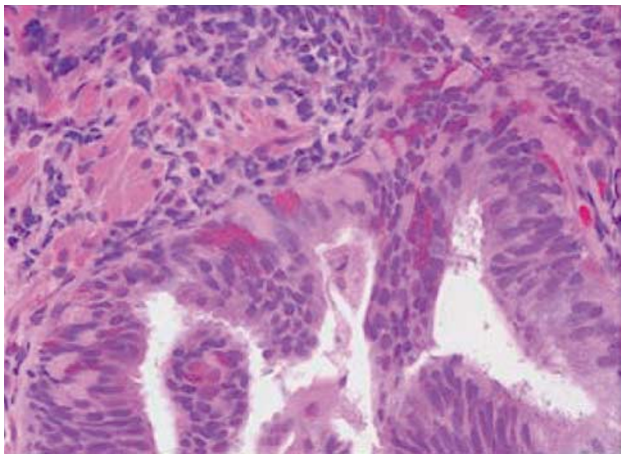

Figure 7 High-grade PIN with neuroendocrine cells (Paneth cell-like change).

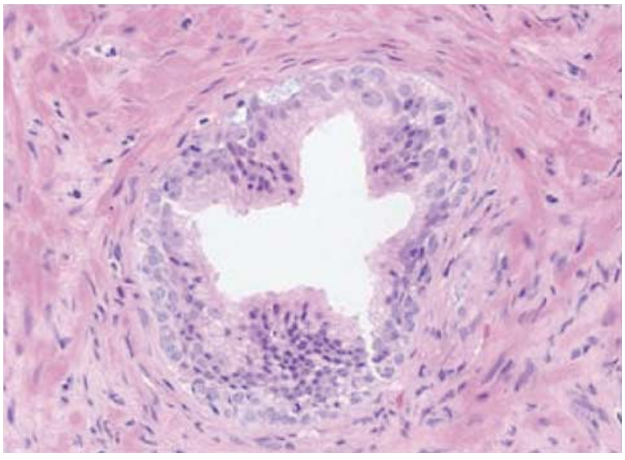

Figure 8 High-grade PIN with basal cell hyperplasia.

prostate biopsies following therapy such as radiation therapy may be one of the most useful roles for antikeratin 34β-E12 (see below).[85]

In addition to PIN and cancer, basal cell layer disruption or loss also occurs in inflamed acini, atypical adenomatous hyperplasia, and postatrophic hyperplasia, and may be misinterpreted as cancer if one relies exclusively on the immunohistochemical profile of a suspicious focus. Furthermore, basal cells of Cowper's glands may not express keratin 34β-E12,[86] although this has been disputed.[87] Rare (0.2%) cases of adenocarcinoma have been reported that express keratin 34β-E12, including foci of metastatic high-grade adenocarcinoma; these cases did not appear phenotypically to be basal cell/adenoid cystic carcinoma.[88]

Basal cell hyperplasia is a histologic mimic of cancer, and use of antikeratin 34β-E12 is recommended in any equivocal cases that include this lesion in the differential considerations.[89–91]

CK5 and CK14 mRNA and protein are expressed in the basal cells of benign acini and PIN, and CK14 mRNA is present in low levels in the luminal cells of the most of some foci of PIN; thus, if PIN is derived from basal cells, as currently believed, CK14 translation is depressed and a low level of CK14 mRNA may persist.[92] CK8 mRNA and protein were constitutively expressed in all epithelia of normal and abnormal prostate tissues. CK19 mRNA and protein were expressed in both basal and luminal cells of benign acini. CK16 mRNA was expressed in a similar pattern as CK19, but CK16 protein was not detected.[92]

We routinely generate unstained intervening sections of all prostate biopsies for possible immunohistochemical staining, recognizing that small foci of concern are often lost when the tissue block is recut; one study reported loss of the suspicious focus in 31 of 52 cases.[93]

Other markers of basal cells include proliferation markers, differentiation markers, and genetic markers. The preferential localization of many of these markers in basal cells but not in secretory cells suggests that they play a role in growth regulation. P63 is a recently introduced nuclear marker that may be useful for separating PIN and cancer from benign mimic; however, experience with this is limited to date, and caution is urged owing to concerns with false-positive and false-negative staining. Basal cells display immunoreactivity at least focally for keratins 5, 10, 11, 13, 14, 16, and 19; of these, only keratin 19 is also found in secretory cells.[94–97] Keratins found exclusively in the secretory cells include 7, 8, and 18. Basal cells usually do not display immunoreactivity for prostate-specific antigen (PSA), prostatic acid phosphatase (PAP), and S-100 protein, and only rare single cells stain with chromogranin and neuron-specific enolase. Conversely, the normal secretory luminal cells invariably stain with PSA and PAP. Prostatic basal cells do not usually display myoepithelial differentiation,[96,98] in contrast with basal cells in the breast, salivary glands, pancreas, and other sites.

A new molecular marker, racemase (alpha-methylacyl-CoA racemase, P504S) was introduced for separating benign and neoplastic acini. This marker has proven useful for evaluation of ASAP (atypical small acinar proliferation suspicious for but diagnostic of cancer) and separation of cancer from hormonally treated benign acini. Its advantage over antikeratin 34β-E12 is its positive granular cytoplasmic staining in cancer cells, with little or no staining in benign acini. The gene for alpha-methylacyl-CoA racemase (AMACR) is greatly overexpressed in prostate cancer cells. AMACR is a well-characterized enzyme that catalyzes the conversion of several (2R)-methyl-branched-chain fatty acyl-CoAs to their (S)-stereoisomers. Analysis of mRNA levels of AMACR revealed an average upregulation of ninefold in prostate cancer. Other reports have substantiated the differential expression of this enzyme protein in benign and cancerous prostate tissues by immunohistochemistry.

Genetic and Molecular Changes

High-grade PIN and prostate cancer share similar genetic alterations.[1,99–102] For example, the frequent 8p12–21 allelic loss commonly found in prostate cancer was also found in microdissected PIN.[99] Other examples of genetic changes found in carcinoma that already exist in PIN include loss of heterozygosity (LOH) at 8p22, 12pter–p12, 10q11.2,[21,99] and gain of chromosomes 7, 8, 10, and 12.[103] Alterations in oncogene bcl2 expression and RER+ phenotype are similar for PIN and prostate cancer.[104,105] In summary, these clinical and molecular studies taken together provide strong evidence that high-grade PIN is the main precursor of prostate cancer. The presence of high-grade PIN alerts both the clinician and the patient that progression to clinically significant prostate cancer is likely.

PIN is associated with progressive abnormalities of phenotype and genotype, which are intermediate between normal prostatic epithelium and cancer, indicating impairment of cell differentiation and regulatory control with advancing stages of prostatic carcinogenesis.[106] There is progressive loss of some markers of secretory differentiation, including prostate-specific antigen, prostatic acid phosphatase, secretory proteins,[94] cytoskeletal proteins,[94] glycoproteins such as blood group antigens, neuroendocrine cells, p-cadherin,[107] fibroblast growth factor-2,[108] inhibin,[109] prostate-specific transglutaminase,[110] androgen receptor expression,[111] insulin-like growth factor binding protein-3,[112] and telomerase.[113] A member of the CIP/KIP family of cyclin-dependent kinase inhibitory proteins, p27KIP1, also showed significant reduction in expression in PIN, cancer, and metastatic cancer when compared with benign prostatic epithelium.[114] Other markers show progressive increase, including including human glandular kallikrein 2 (hK2),[115] c-erbB-2 (Her-2/neu) and c-erbB-3 oncoproteins,[108,116] c-met proto-oncogene,[41] bcl-2 oncoprotein,[117,118] mutator (RER(+)) phenotype,[104] epidermal growth factor and epidermal growth factor receptor,[108,119] type IV Collagenase, Lewis Y antigen, TGF-alpha, apoptotic bodies,[71,73,104] mitotic figures,[71] PCNA expression, Ki-67 expression, MIB-1 expression,[111] tenascin-C,[120] aneuploidy and genetic abnormalities,[62,111,121–127] microvessel density, Ep-Cam transmembrane glycoprotein,[128] Insulin-like growth factor binding protein IGFBP-rP1, and p53 mutations,[129] although one group found no p53 expression immunohistochemically in PIN.[130] Prostate-specific membrane antigen, an abundant transmembrane glycoprotein, shows increased expression in PIN and cancer when compared with benign epithelium,[131,132] and this expression was unaffected by short-term androgen deprivation therapy.[132] Estrogen receptor alpha is present in up to 28% of cases of PIN and 43% of cancers, but estrogen receptor beta is absent;[133] prolactin receptor expression is increased in PIN.[134]

A model of prostatic carcinogenesis has been proposed based on the morphologic continuum of PIN and the multistep theory of carcinogenesis.[1]

Microvessel density is increased In PIN

PIN is virtually always accompanied by a proliferation of small capillaries in the stroma, despite separation from the underlying vasculature by a basal cell layer and basement membrane. It is likely that PIN initially coopts adjacent vessels, similar to other tumors, and that these vessels soon regress, only to be followed by vigorous angiogenesis at the cancer's edge. A critical balance exists between the proangiogenic vascular endothelial growth factor and the angiogenic antagonist angiopoietin-2.

Microvessel density is higher in high-grade PIN than in adjacent benign prostatic tissue, and the capillaries are shorter, more widely spaced, have more open lumina and curvaceous external contours, and are lined by a greater number of endothelial cells. The degree of microvessel density in PIN is intermediate between benign epithelium and cancer, lending support to the concept of PIN as the precursor of prostate cancer. Inhibition of angiogenesis may be an effective method of chemoprevention, particularly for men at high risk such as those who have high-grade PIN. It should be well tolerated in most adults because angiogenesis under typical conditions is needed only for reproduction and wound healing.[65]

Animal Models of PIN and Prostate Cancer

Several different animal models of prostate cancer have demonstrated that high-grade PIN is in the direct causal pathway to prostate cancer.[135] The transgenic mouse model of prostate cancer (TRAMP) has been shown to mimic human prostate cancer.[136,137] In the TRAMP model, the Probasin promoter-SV40 large T antigen (PB-Tag) transgene is expressed specifically in the epithelial cells of the murine prostate under the control of the probasin promoter. The probasin promoter is androgen-dependent. As a result, this model has several advantages over currently existing models: (1) mice develop progressive forms of prostatic epithelial hyperplasia and high-grade PIN as early as 10 weeks and invasive prostate adenocarcinoma around 18 weeks of age;[136] (2) the pattern of metastatic spread of prostate cancer mimics that of human prostate cancer with common sites of metastases being lymph node, lung, kidney, adrenal gland and bone; (3) the development as well as the progression of prostate cancer can be followed within a relatively short period of 10–30 weeks; (4) spontaneous prostate tumors arise with 100% frequency; and (5) animals may be screened for the presence of the prostate cancer transgene prior to the onset of clinical prostate cancer. Another animal model is the transgenic mouse model that contains a probasin

promoter that controls the ECO:R1 gene. This gene product has been implicated in the induction of genomic instability.[138] Prostates from these animals were followed prospectively from 4 to 24 months of age and showed the progressive presence of mild to severe hyperplasia, low-grade PIN, high-grade PIN, and then well-differentiated adenocarcinoma of the prostate.[138] Stanbrough *et al*[139] demonstrated that transgenic mice that have prostatic overexpression of AR protein develop focal areas of high-grade PIN.

The mechanism of prostate carcinogenesis appears to involve estrogenic signaling. Wang *et al*[140] treated wild-type mice with testosterone propionate and estradiol for 4 months. These mice developed prostatic hyperplasia, high-grade PIN, and invasive prostate cancer. When α-ERKO mice, mice that have the ERα genetically knocked out, are treated the same way, they develop prostatic hyperplasia, but not high-grade PIN or invasive prostate cancer.[140] Similarly, a prospective, placebo-controlled study of TRAMP mice treated with an antiestrogen, Acapodene (toremifene) was performed to pharmacologically antagonize ERα. These acapodene-treated TRAMP mice had a reduction in high-grade PIN, significant decrease in prostate cancer incidence, and an increase in animal survival. Thus, estrogenic signally through ERα may play a key role;[30] prostate carcinogenesis and that high-grade PIN was observed to be in the direct causal pathway to prostate cancer.

The dog is the only nonhuman species in which spontaneous prostate cancer occurs, and, like humans, the rate of canine prostate cancer increases with aging.[141–145] High-grade PIN has been also observed in the prostates of these animals.[142–145] Canine high-grade PIN shows cytological features identical to the human counterpart, including cell crowding, loss of polarity, and nuclear and nucleolar enlargement. Like prostatic adenocarcinoma, high-grade PIN also increases with aging.[142] High-grade PIN appears to represent an early event in prostate carcinogenesis that occurs with high frequency within the prostates of pet dogs sharing the same environment as humans. In this model, high-grade PIN was determined to be an intermediate step between benign epithelium and invasive carcinoma. Thus, like the transgenic mouse models, the canine model supports high-grade PIN as part of a continuum in the progression of prostate cancer.

Clinical significance of PIN

PIN does not Elevate PSA

Biopsy remains the definitive method for detecting PIN and early invasive cancer, but noninvasive methods, including serum tests, are being evaluated. Serum PSA concentration may be elevated in patients with PIN,[146] although these results have been refuted.[147,148] There is a poor correlation of PIN and PSA density according to studies of radical prostatectomy specimens and preoperative serum.[148] Mean PSA increased from 8.4 to 11.6 ng/ml in patients with PIN who developed cancer within two years; those with PIN who did not develop cancer during this interval had an increase in PSA from 4.8 to 5.9 ng/ml or decrease from 5.1 to 4.6 ng/ml; however, these findings have not been confirmed.

The ratio of free to total PSA is the same for patients with high-grade PIN and cancer, unlike low-grade PIN and hyperplasia, although this has also been refuted. Many patients in these studies were later found to have cancer, so the elevation in serum PSA concentration and its derivatives may have resulted from the undetected cancer.

Transrectal Ultrasound cannot Detect PIN

By transrectal ultrasound, PIN may be hypoechoic like carcinoma, although these findings have not been confirmed.[32] Today, most urologists and radiologists do not believe that PIN is detectable by transrectal ultrasound because PIN is a microscopic finding which is below the detection threshold for this form of imaging.

Men with PIN Develop Prostate Cancer

The predictive value of high-grade PIN was evaluated in a retrospective case–control study of 100 patients with sextant needle biopsies with high grade PIN and 112 biopsies without PIN matched for clinical stage, patient age, and serum PSA.[149] Adenocarcinoma was identified in 36% of subsequent biopsies from cases with PIN, compared with 13% in the control group. The likelihood of finding cancer increased as the time interval from first biopsy increased (32% incidence of cancer within 1 year, compared with 38% incidence in follow-up biopsies obtained after more than 1 year). High-grade PIN, patient age, and serum PSA concentration were jointly highly significant predictors of cancer, with PIN providing the highest risk ratio (14.9). Other series have also found a high predictive value of PIN for cancer, although recent reports based on obtaining a greater number of cores shows a lower predictive value (Table 4).[51,54–56,150–158] These data underscore the strong association of PIN and adenocarcinoma and indicate that vigorous diagnostic follow up is needed.

High-grade PIN in transurethral resection specimens is also an important predictive factor for prostate cancer.[159,55] Among 14 patients with PIN and BPH followed for up to 7 years (mean, 5.9 years), three (21.4%) developed prostatic cancer.[159] Mean serum PSA concentration was higher than in those who did not develop cancer (8.1 *vs* 4.6 ng/ml, respectively). All subsequent cancers apparently arose in the peripheral zone and were detected by needle biopsy. Thus, all tissue should be submitted

Table 4 Cancer detection in patients with high-grade PIN

Reference	*Pt. population*	*No. of men*	*% patients with cancer on repeat biopsy*	*Control group?*	*Comment*
Brawer *et al*[56]	Urology practice	10	100	No	Small study; no control group
Ellis and Brawer[150]	Urology practice	5	100	No	Small study; no control group
Aboseif *et al*[181]	Urology practice	24	79.1	No	Small study; no control group
Weinstein and Epstein[151]	Urology practice	19	53	No	Small study; no control group
Keetch *et al*[152]	PSA screening	37	51	Yes; patients benign biopsies	Number of foci of PIN and linear extent were not predictive of cancer
Davidson *et al*[149]	Two urology practices	100	35	Yes; matched patients with benign biopsy	Pt. age older than 65 yearr and serum PSA >4 ng/ml increased risk of later cancer
Markham[153]	Urology practice	32	41	No	Diagnosis of PIN based on fine-needle aspiration
Raviv *et al*[182,154]	Urology practice	48	47.9	Yes; patients without cancer on repeat biopsy	DRE and PSA increased risk of later cancer; PSA density not helpful
Langer *et al*[51]	Urology practice	53	27	No	No difference in pt. age, PSA, or interval to repeat biopsy between those with and without cancer
Berner *et al*[183]	Oncology practice	37	38	Patients with BPH	No difference in DNA ploidy status between those with subsequent cancer and those without
Shepherd *et al*[157]	PSA screening	66	58	No	Quadrant location of PIN and cancer matched in only 35% of cases
Perachino *et al*[54]	Urology practice	21	71.1	Patients without PIN	
Krishnamurthi *et al*[184]	Urology practice	74	31	No	No difference in detection rate for cancer by age, abnormal DRE, TRUS, PIS velocity, or length of follow-up
Rovner *et al*[185]	Urology practice	19	31.6	Patients without PIN	Transurethral biopsy was of no diagnostic value
Park *et al*[186]	Urology practice	43	51	No	Men with atypia or high-grade PIN merit close follow-up
Park *et al*[158]	Urology practice	104	22	No	PSA velocity, and DRE and TRUS findings at initial biopsy were independent predictors of malignant disease on repeat biopsy
Kronz *et al*[187]	Urology practice	245	32	No	The only independent histologic predictor of a cancer diagnosis was the number of cores with high-grade PIN
Igel *et al*[188]	Urology practice	88	43	No	Only independent variable predictive of positive biopsy was prostate volume

by the pathologist for examination when high-grade PIN is found in TURP specimens. The high predictive value of PIN for the development of subsequent cancer warrants reporting the presence of PIN in TURP specimens, according to the Cancer Committee of the College of American Pathologists. Conversely, a recent report showed that PIN in the transition zone and central zone from Norwegian men is not predictive of subsequent cancer development.[160]

Androgen Deprivation Therapy Eliminates PIN

There is a marked decrease in the prevalence and extent of high-grade PIN in cases after androgen deprivation therapy when compared with untreated cases.[161–163] This decrease is accompanied by epithelial hyperplasia, cytoplasmic clearing, and prominent glandular atrophy, with decreased ratio of glands to stroma. These findings indicate that the dysplastic prostatic epithelium is hormone dependent. In the normal prostatic epithelium, luminal secretory cells are more sensitive to the absence of androgen than basal cells, and these results indicate that the cells of high-grade PIN share this androgen sensitivity. The loss of some normal, hyperplastic, and dysplastic epithelial cells with androgen deprivation is probably due to acceleration of programmed single cell death. A recent report suggested that PIN is not substantially decreased after hormonal therapy, but those authors failed to use current criteria for PIN, so the results are not comparable.[164]

Neoadjuvant hormone deprivation with monthly leuprolide and flutamide 250 mg p.o. t.i.d. for 3 months resulted in a 50% reduction in high-grade PIN. Longer therapy with 6 months of neoadjuvant androgen deprivation therapy prior to radical prostatectomy in the European Randomized Study of Screening for Prostate Cancer (ERSPC) study reduced high-grade PIN even more.[23] Flutamide decreased the prevalence and extent of high-grade PIN and induced epithelial atrophy.[165] There is also evidence that cessation of flutamide resulted in return of high-grade PIN.[16,166]

The results of 5-alpha-reductase (finasteride) treatment in high-grade PIN are controversial and the cumulative number of cases studied is probably too small to draw firm conclusions. Two reports found no apparent effect on the histologic appearance or extent of high-grade PIN,[167,168] whereas a third study of three cases described atrophy and involution with decreased prevalence.[169]

Radiation Therapy Eliminates PIN

The prevalence and extent of PIN is decreased after radiation therapy.[170–172] However, one study paradoxically noted a higher incidence (70%) of PIN after radiation therapy than expected,[171] but they failed to employ accepted diagnostic criteria for PIN, so their results are not comparable with others. A recent report from Memorial Sloan-Kettering found PIN in 8.8% of biopsies following a course of three-dimensional external beamconformal radiation therapy.[172]

Following radiation therapy, PIN retains the features characteristic of untreated PIN, and is readily recognized in tissue specimens. The key pathologic features include nuclear crowding, nuclear overlapping and stratification, nuclear hyperchromasia, and prominent nucleoli. The basal cell layer is present, but often fragmented. The most common patterns of PIN are tufting and micropapillary, similar to those reported in untreated PIN.

The long-term efficacy of radiation treatment may depend on eradication of cancer as well as precancerous lesions that may otherwise lead to evolution of secondary metachronous invasive cancers. Identification of residual or recurrent cancer portends a worse prognosis. The questions remain whether recurrent cancer after irradiation is due to regrowth of incompletely eradicated tumor or progression from incompletely eradicated PIN. Further studies of salvage prostatectomy specimens and post-RT needle biopsies are justified in an attempt to establish the significance of high-grade PIN as a source of long-term treatment failure among these patients. If PIN is associated with treatment failure, adjuvant chemoprevention strategies that ablate this lesion may reduce the risk of late cancer recurrence.

Should Men with High-grade PIN be Treated?

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, so its identification in biopsy specimens warrants further search for concurrent invasive carcinoma. If all procedures fail to identify coexistent carcinoma, close surveillance and follow-up are indicated. As high-grade PIN progresses, the likelihood of basal cell layer disruption increases, very much like what is observed for carcinoma *in situ* (CIS) of the urinary bladder. CIS of the urinary bladder, like PIN, may become invasive and is treated aggressively. The standard of care for management of CIS of the bladder is intravesical instillation of chemotherapy or BCG, and, in some cases, radical cystectomy.

Follow-up biopsy is suggested at 3–6-month intervals for 2 years, and thereafter at 12-month intervals for life.[149,173] Some urologists have performed 'saturation' biopsies, consisting of more than 12–15 biopsies in one session, often with brief general anesthesia in the operating theatre, in an effort to definitively exclude cancer. Most authors agree that the identification of PIN in the prostate should not influence or dictate therapeutic

decisions.[173] We are aware of 21 radical prostatectomies that were purposely (three cases) or inadvertently performed (18 cases) in patients whose biopsies contained only high-grade PIN; all but two of the cases contained adenocarcinoma in the surgical specimen (DG Bostwick, personal communication, 2003).

Currently, routine treatment is not available for patients who have high-grade PIN. Prophylactic radical prostatectomy or radiation is not an acceptable treatment for patients who have high-grade PIN only.[174] The development and identification of acceptable agents to treat high-grade PIN would fill a therapeutic void. As noted above, androgen deprivation therapy and radiation therapy induce acinar atrophy and apoptosis that result in regression of high-grade PIN.[70,161–163,169,174–176]

Chronic therapy, however, would most likely be required to prevent new high-grade PIN lesions from invading and becoming clinical prostate cancer. Although more toxicity is likely to be tolerated for the treatment agents targeted to regress or inhibit high-grade PIN, as compared to treating healthy patients to reduce prostate cancer incidence, androgen deprivation therapy has too many adverse effects in men to be clinically useful. Newer agents with better safety and lower side effect profile are greatly needed since patients may be taking the agent at least until they attain 70 years of age.[174] Acapodene, an antiestrogen is currently in a Phase IIb multicenter, randomized, prospective placebo-controlled human clinical trial to determine if it can treat high-grade PIN and reduce prostate cancer incidence; preliminary results are encouraging.[30]

PIN offers promise as an intermediate end point in studies of chemoprevention of prostatic carcinoma. 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 noninvasive precursor lesion PIN is a suitable intermediate histologic marker to indicate subsequent likelihood of cancer.

PIN Predicts Cancer Recurrence

PIN was not predictive of PSA (biochemical) failure at 32 months in patients undergoing radical prostatectomy and androgen deprivation therapy.[161]

Differential diagnosis of PIN

The histologic differential diagnosis of PIN includes lobular atrophy, postatrophic hyperplasia, atypical basal cell hyperplasia (Figure 9), cribriform hyperplasia (Figure 10), and metaplastic changes

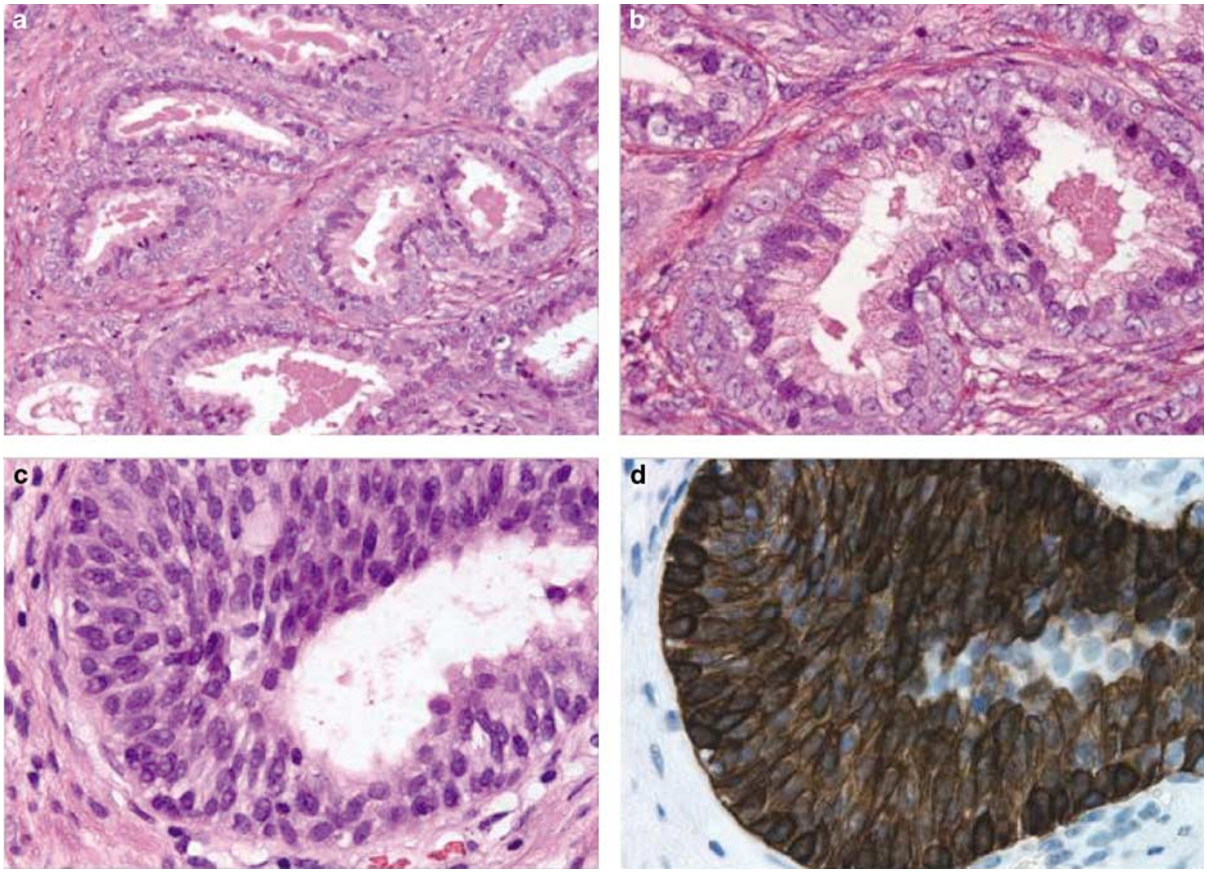

Figure 9 Atypical basal cell hyperplasia (**a–c**). (**d**) Immunostain for 34β12 reveals strong basal cell staining.

associated with radiation (Figure 11), infarction, and prostatitis. Many of these display architectural and cytologic atypia, including enlarged nucleoli, and small specimens, and cauterized or distorted specimen. Cribriform adenocarcinoma, ductal (endometrioid) carcinoma, and urothelial carcinoma involving prostatic ducts and acini may also be confused with PIN (Figure 12). Biopsies submitted with incomplete patient history should be interpreted with caution.

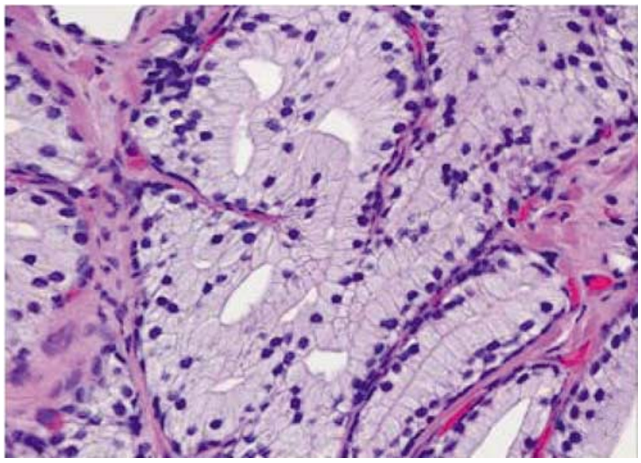

Figure 10 Clear cell cribriform hyperplasia showing bland cytology and basal cell layer around the gland.

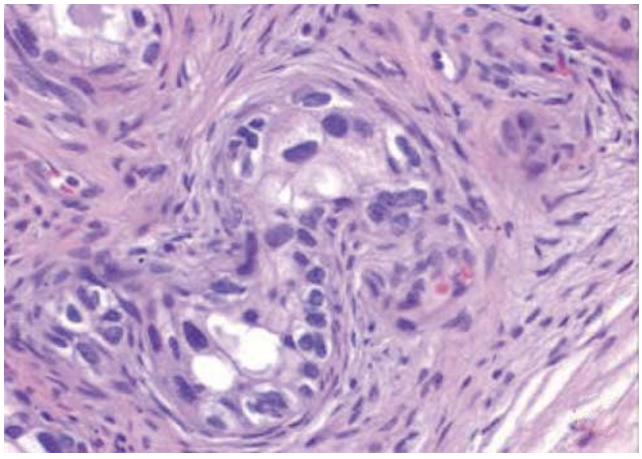

Figure 11 Benign prostatic tissue with radiation changes.

PIN may be overdiagnosed as adenocarcinoma. A retrospective review of transurethral resections from the Mayo Clinic files between 1960 and 1970 revealed that PIN was often diagnosed as adenocarcinoma.[177] Similarly, fine-needle aspiration of the prostate may yield cell clusters of PIN that are overdiagnosed as cancer; this issue is critically important to consider in evaluating studies from Sweden and other countries that have, perhaps erroneously, relied on fine-needle aspiration diagnoses for patients treated with watchful waiting (expectant management).

Conclusion

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, which 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.

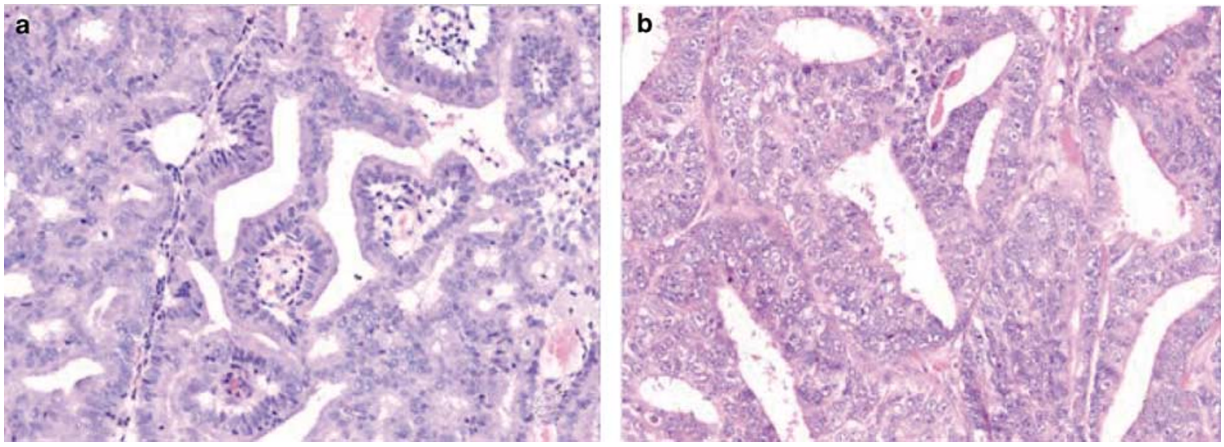

Figure 12 Ductal/papillary carcinoma.

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