High-Grade Prostatic Intraepithelial Neoplasia

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High-grade prostatic intraepithelial neoplasia is considered the most likely precursor of prostatic carcinoma. The only method of detection is biopsy; prostatic intraepithelial neoplasia (PIN) does not significantly elevate serum prostate-specific antigen concentration and cannot be detected by ultrasonography. The incidence of PIN in prostate biopsies averages 9% (range, 4%-16%), representing 115,000 new cases of PIN diagnosed each year in the United States. PIN has a high predictive value as a marker for adenocarcinoma, and its identification warrants repeated biopsy for concurrent or subsequent invasive carcinoma. Carcinoma will develop in most patients with PIN within 10 years. 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. 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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Key words: Prostatic intraepithelial neoplasia • Prostate cancer • Alpha-methylacyl-CoA racemase • Androgen deprivation therapy

Prostatic intraepithelial neoplasia (PIN) represents the preinvasive end of the continuum of cellular proliferations within the lining of prostatic ducts and acini. The term "PIN" is usually used today as a synonym for high-grade PIN (HGPIN) (formerly PIN grades 2 and 3 on a 1-3 scale). The high level of interobserver variability with low-grade PIN limits its clinical utility, and pathologists do not routinely report this finding except in research studies.[1] Interobserver agreement

Table 1
Estimated Frequency of High-Grade PIN in the United States

Age (y)	No. US Population*	High-Grade PIN (%)
40-49	20,550,000	3,123,600 (15.2)
50-59	14,187,000	3,404,880 (24.0)
60-69	9,312,000	4,404,576 (47.3)
70-79	6,926,000	4,044,784 (58.4)
80-89	2,664,000	1,864,800 (70.0)
Total	**53,639,000**	**16,842,640**

*1990 US census.
PIN, prostatic intraepithelial neoplasia.

for HGPIN is "good to excellent."[2] Other terms, such as "dysplasia," "carcinoma in situ," and "intraductal carcinoma," are discouraged.

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. The incidence of isolated HGPIN averages 9% (range, 4%-16%) of prostate biopsies, representing 115,000 new cases of HGPIN without cancer diagnosed each year (Table 1).

The incidence and extent of PIN appear to increase with patient age (Table 1).[3,4] 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.[4] 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.[4]

Table 2
Incidence of Isolated High-Grade PIN in Prostatic Needle Biopsies

Reference	Patient Population	Men, N	Incidence of PIN (%)
Screening Programs			
Mettlin et al, 1991[37]	American Cancer Society National Prostate Cancer Detection Project	330	5.2
Feneley et al, 1997[38]	Screening population in Gwent, England, 1991-1993	212	20
Hoedemaeker et al, 1999[39]	PSA screening study in Rotterdam, The Netherlands	1824	0.7
Urology Practice			
Lee et al, 1989[40]	Consecutive biopsies of hypoechoic lesions at St. Joseph Mercy Hospital	256	11
Bostwick et al, 1995[41]	Consecutive biopsies at Mayo Clinic	200	16.5
Bostwick et al, 1995[41]	Consecutive biopsies at Glendale Hospital, Calif	200	10.5
Langer et al, 1996[42]	Consecutive biopsies at University of Pennsylvania Medical Center	1275	4.4
Wills et al, 1997[43]	Consecutive biopsies at Johns Hopkins Hospital	439	5.5
Feneley et al, 1997[38]	Consecutive biopsies at University College London Hospitals, 1988-1994	1205	11
O'Dowd et al, 2000[44]	Consecutive biopsies at UroCor Labs, Okla, 1994-1998	132,426	2.3
Fowler et al, 2001[45]	Consecutive biopsies of men with suspected carcinoma at the Veterans Affairs Medical Center, Miss, 1992-1998	1050	8.9

Note: Table 2 is restricted to larger studies, with an arbitrary cutoff of N ≥ 200.
PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen.

Table 3
Incidence of Isolated High-Grade PIN in Prostatic Transurethral Resections

Reference	Patient Population	Men, n	Incidence of PIN (%)
Gaudin et al, 1997[46]	Consecutive TURPs without cancer at Johns Hopkins Hospital	158	3.2
Pacelli and Bostwick, 1997[47]	Consecutive TURPs without cancer at Mayo Clinic	570	2.8
Skjorten et al, 1997[48]	Consecutive TURPs from 1974-1975 at Ullevaal and Lovisenberg Hospitals, Oslo, Norway	731	33

PIN, prostatic intraepithelial neoplasia; TURP, transurethral resection of the prostate.

Most foci of PIN in young men are low grade, with increasing frequency of HGPIN with advancing age. The volume of HGPIN also increases with patient age.[3]

Race and geographic location may also influence the incidence of HGPIN.[1] For example, African American men have a greater prevalence of HGPIN than whites in the 50- to 60-year age group. In contrast, Japanese men living in Osaka, Japan, have a significantly lower incidence of HGPIN than men residing in the United States, and Asians have the lowest clinically detected rate of prostate cancer.[5] Interestingly, Japanese men with HGPIN also had an increased likelihood of prostate cancer developing, suggesting that HGPIN is a precursor of clinical prostate cancer in Asian men, too. Thus, the differences in the frequency of HGPIN in the 50- to 60-year age group across races essentially mirror the rates of clinical prostate cancer observed in the 60- to 70-year age group.

The causal association of HGPIN with prostatic adenocarcinoma is based on the fact that the prevalence of both HGPIN and prostate cancer increases with patient age and that HGPIN precedes the onset of prostate cancer by less than 1 decade (Table 1). The severity and frequency of HGPIN in prostates with cancer are greatly increased (73% of 731 specimens) compared with that of prostates without cancer (32% of 876 specimens).[3,6]

Incidence of PIN

The incidence of PIN varies according to the population of men under study (Table 2). The lowest likelihood is in men participating in PSA screening and early detection studies, with an incidence of PIN detected on biopsy ranging from 0.7% to 20%. Men seen by urologists in practice show PIN in 4.4% to 25% of contemporary needle biopsy samples. Those undergoing transurethral resection have the highest likelihood of PIN, from 2.8% to 33% (Table 3).

Diagnostic Criteria for PIN

PIN is characterized by cellular proliferations within preexisting ducts and acini with cytologic changes mimicking cancer, including nuclear and nucleolar enlargement. There is inversion of the normal orientation of epithelial proliferation with PIN from the basal cell compartment to the luminal surface, similar to adenomas in the colon and other sites. Four main patterns of HGPIN have been described: tufting, micropapillary, cribriform, and flat[7] (Figures 1-4). There are no known clinically important differences between the architectural patterns, and their recognition appears to be only of diagnostic utility. Other unusual patterns of PIN include the signet ring cell pattern, small cell neuroendocrine pattern, mucinous pattern, and microvacuo-

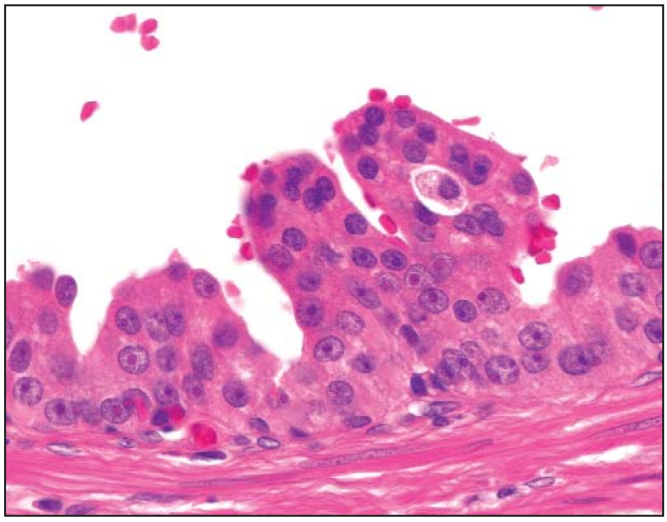

Figure 1. *High-grade prostatic intraepithelial neoplasia, tufting pattern (hematoxylin & eosin, × 400).*

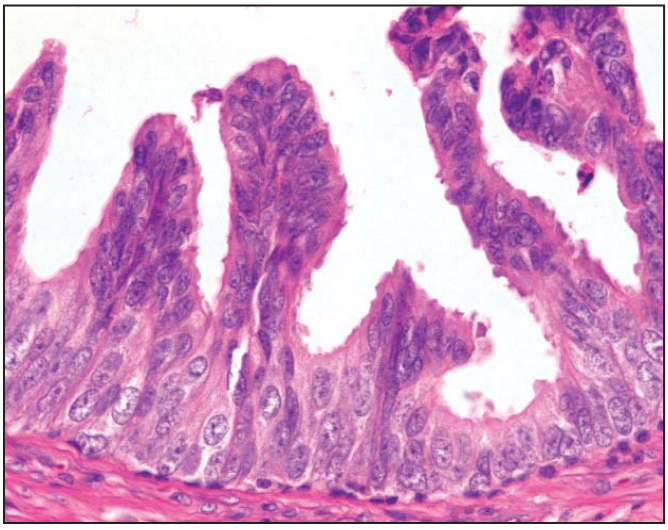

Figure 2. *High-grade prostatic intraepithelial neoplasia, micropapillary pattern (hematoxylin & eosin, × 400).*

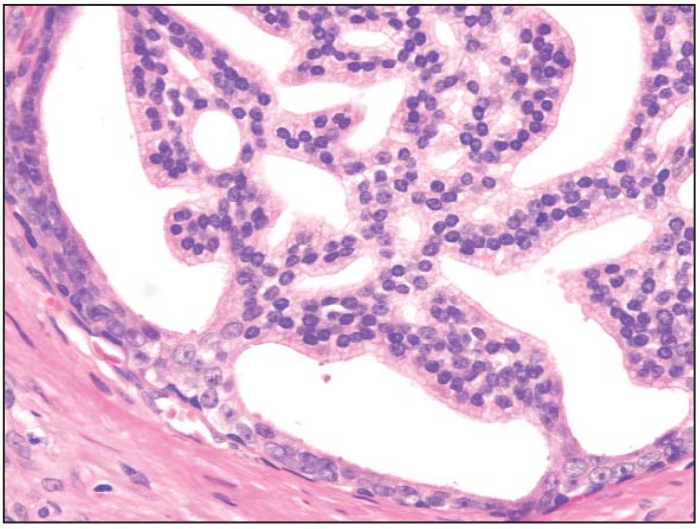

Figure 3. *High-grade prostatic intraepithelial neoplasia, cribriform pattern (hematoxylin & eosin, × 200).*

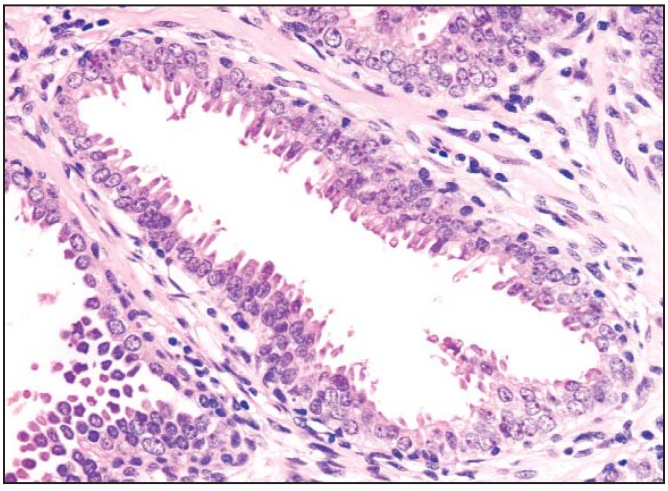

Figure 4. *High-grade prostatic intraepithelial neoplasia, flat pattern (hematoxylin & eosin, × 200).*

lated (foamy gland) pattern, and inverted (hobnail) pattern.[1]

Early stromal invasion, the earliest evidence of carcinoma, occurs at sites of acinar outpouching and basal cell disruption in acini with HGPIN. Such microinvasion is present in about 2% of high-power microscopic fields of PIN and is seen with equal frequency in all architectural patterns.[8]

HGPIN, like cancer, is usually multicentric[3,8,9] and most commonly found in the peripheral zone of the prostate. The volume of HGPIN in prostates with cancer increases with increasing pathologic stage, Gleason grade, positive surgical margins, and perineural invasion.[3] These findings underscore the close spatial and biologic relationship between PIN and cancer.

Because of the inability to separate tangential cutting of the larger preexisting acini of PIN (which may appear as small, separate, adjacent acini) from the smaller discrete acini of cancer in needle biopsy specimens, an equivocal diagnosis (atypical small acinar proliferation suspicious for but not diagnostic of malignancy) has to be rendered.

Diagnostic Immunohistochemistry of PIN

Select antibodies such as anti-keratin 34ß-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.

Monoclonal basal cell–specific anti-keratin 34ß-E12 is the most commonly used immunostain for prostatic basal cells.[10] According to studies utilizing anti-keratin 34ß-E12, increasing grades of PIN are associated with progressive disruption of the basal cell layer. Early invasive carcinoma occurs at sites of glandular outpouching and basal cell discontinuity in association with PIN.[11] Cancer cells consistently fail to react with this antibody, although rare (0.2%) cases of adenocarcinoma that express keratin 34ß-E12 have been reported.[12] Thus, immunohistochemical stain for anti-keratin 34ß-E12 plays an important role in separating cancer from its mimics, including cribriform pattern of PIN, basal cell hyperplasia, inflamed acini, atypical adenomatous hyperplasia, post-atrophic hyperplasia, and radiation treatment changes.

Other markers of basal cells include proliferation markers, differentiation markers, and genetic markers. p63 is a recently introduced nuclear marker that may be useful for separating PIN and cancer from benign mimics. Keratins 5, 10, 11, 13, 14, 16, and 19 are immunoreactive at least focally in basal cells; of these, only keratin 19 is also found in secretory cells.[13] Keratins found exclusively in the secretory cells include 7, 8, and 18. Basal cells usually do not display immunoreactivity for PSA, prostatic acid phosphatase (PAP), and S-100 protein. Conversely, the normal secretory luminal cells invariably stain with PSA and PAP.

A new molecular marker, alpha-methylacyl-CoA racemase (P504S), was introduced for separating benign and neoplastic acini. Its advantage over anti-keratin 34ß-E12 is its positive cytoplasmic staining in cancer cells, with little or no staining in benign acini. Current reports have substantiated the differential expression of this enzyme protein in benign and cancerous prostate tissues by immunohistochemistry.[14]

Genetic and Molecular Changes

HGPIN and prostate cancer share similar genetic alterations.[15] For example, the frequent 8p12-21 allelic loss commonly found in prostate cancer was also found in microdissected PIN.[15] Other examples of genetic changes found in carcinoma that already exist in PIN include loss of heterozygosity at chromosomes 6 and 8, decrease in telomere length,[16] and gain of chromosomes 7, 8, 10, and 12.[17] Recently, by cDNA microarray containing 8700 features, Calvo and coworkers[18] have identified more than 400 genes abnormally expressed in both HGPIN and prostate cancer. In summary, these molecular studies indicate that the presence of HGPIN 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. There is progressive loss of some markers, such as PSA, PAP, cytoskeletal proteins, and annexin I protein.[19] Other markers show progressive increase, such as c-erbB-2 (Her-2/neu) and c-erbB-3 oncoproteins, c-met proto-oncogene, bcl-2 oncoprotein, members of the growth factor family,[20] inducible nitric oxide synthase, alpha-methylacyl-CoA racemase,[14] glycoprotein A-80,[21] and apolipoprotein-D.[22] Furthermore, Henshall and associates[23] found that overexpression of p16INK4A in HGPIN was an independent predictor of disease relapse, providing the first evidence for a prognostic marker in HGPIN.

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. The degree of microvessel density in PIN is intermediate between benign epithelium and cancer, lending support to the HGPIN.

Animal Models of PIN and Prostate Cancer

Several different animal models of prostate cancer have demonstrated that HGPIN is in the direct causal pathway to prostate cancer.[1] The transgenic mouse model of prostate cancer (TRAMP) has been shown to mimic human prostate cancer. 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 HGPIN as early as 10 weeks and invasive prostate adenocarcinoma around 18 weeks of age; 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 to 30 weeks; 4) spontaneous prostate tumors arise with 100% frequency; and 5) animals may be screened for the presence of the prostate cancer transgene before the onset of clinical prostate cancer.

Other specific genes, such as ECO:R1 Nkx3.1, and FGF8b, have been targeted in mouse models resulting in the development of HGPIN.[24] The dog is the only nonhuman species in which spontaneous prostate cancer occurs, and, like in humans, the rate of canine prostate cancer increases with aging.[25] HGPIN also has been observed in the prostates of these animals, with cytologic features identical to those of the human counterpart.[26] Similar to the incidence of prostatic adenocarcinoma, HGPIN incidence also increases with aging.[26] Thus, like the transgenic mouse models, the canine model supports HGPIN 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

Table 4
Cancer Detection in Patients With High-Grade PIN

Reference	Population	Men, N	Patients With Cancer on Repeated Biopsy (%)
Davidson et al[29]	Two urology practices	100	35
Raviv et al[49]	Urology practice	48	47.9
Langer et al[42]	Urology practice	53	27
Shepherd et al[50]	PSA screening	66	58
Kirschenbaum et al[51]	Urology practice	74	31
Park et al[52]	Urology practice	43	51
Kronz et al[30]	Urology practice	245	32
Igel et al[53]	Urology practice	88	43
Vukovic et al[16]	Urology practice	104	22
Gokden et al*	Urology practice	221	28
Sakr et al*	Urology practice	540	27
Siever et al*	Urology practice	145	25
Schlesinger & Bostwick*	Urology practice	335	23

PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen.
Note: Table 4 is restricted to larger studies, with an arbitrary cutoff of N ≥ 40.
*Presented at 2003 United States and Canadian Academy of Pathology meeting.

evaluated. Serum PSA concentration may be elevated in patients with PIN, although this has been refuted.[27] Elevated PSA levels in patients with HGPIN may have resulted from the undetected cancer.

Transrectal Ultrasound Cannot Detect PIN

On transrectal ultrasonograms, PIN may be hypoechoic like carcinoma, although these findings have not been confirmed.[28] Today, most urologists and radiologists do not believe that PIN is detectable by transrectal ultrasound because PIN is a microscopic finding that is below the detection threshold for this form of imaging.

Prostate Cancer Develops in Men With PIN

The predictive value of HGPIN for cancer was evaluated in a retrospective case-control study of 100 patients with sextant needle biopsy results showing HGPIN and 112 with biopsy results without PIN matched for clinical stage, age, and serum PSA level.[29] Adenocarcinoma was identified in 36% of subsequent biopsies from patients 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% in follow-up biopsies performed after more than 1 year).

HGPIN, 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 (Table 4). Kronz and coworkers[30] further found that the number of core samples with HGPIN was the only independent histologic predictor of a cancer diagnosis; risk of cancer was 30.2% with 1 or 2 cores with HGPIN, 40% with 3 cores, and 75% with more than 3 cores. These data underscore the strong association of PIN and adenocarcinoma and indicate that vigorous diagnostic follow-up is needed. Our recent study, however, revealed a 23% predictive value of PIN for prostate cancer, which is comparable to the 25%, 27%, and 28% predictive values reported by

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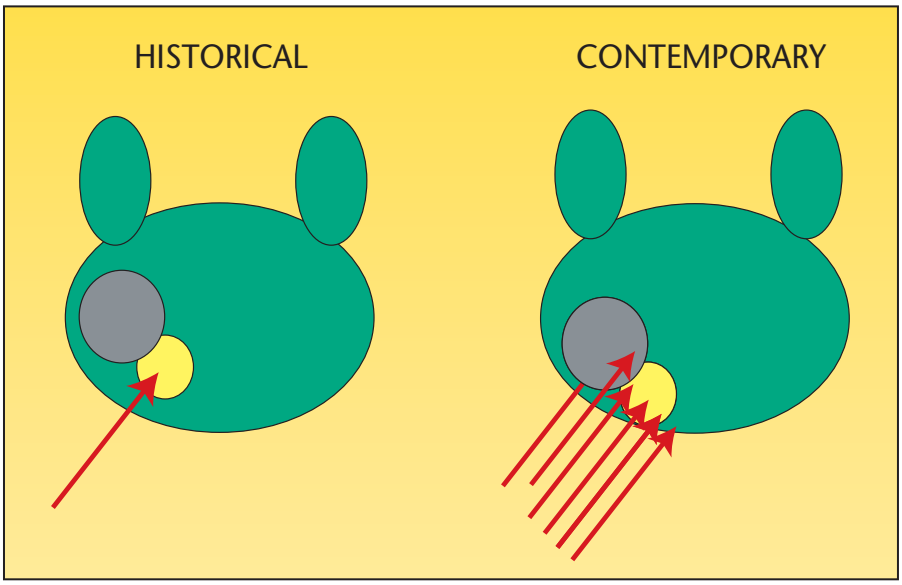

Figure 5. *Historical biopsy approaches (left) could easily miss invasive cancer (gray) because of undersampling. In modern biopsy approaches (right), with multiple cores being taken, it is unlikely that a concomitant carcinoma in the face of PIN (yellow) will be missed. PIN, prostatic intraepithelial neoplasia.*

other groups at the 2003 United States and Canadian Academy of Pathology meeting.

We believe that the following factors account for the decline in predictive accuracies of HGPIN for prostate cancer. The major role is played by use of extended biopsy techniques that result in more thorough prostate sampling and in higher cancer detection rates (Figure 5). Conversely, by these actions there remains a smaller pool of patients to receive isolated diagnoses of PIN. Another contributor is the lower detection rate for and difficulty in the detection of the remaining small cancers; larger significant tumors may also escape detection. These results may reflect a new steady state and a newly reached low plateau in the predictive accuracy of PIN.

Androgen Deprivation Therapy Eliminates PIN

There is a marked decrease in the prevalence and extent of HGPIN after androgen deprivation therapy when compared with untreated cases. This decrease is accompanied by epithelial hyperplasia, cytoplasmic clearing, and prominent glandular atrophy, with a decreased ratio of glands to stroma. These findings indicate that the cells of HGPIN are as hormone-dependent as normal secretory epithelium.

Neoadjuvant hormone deprivation with a monthly dose of leuprolide and flutamide, 250 mg PO tid for 3 months, resulted in a 50% reduction in HGPIN. There is also evidence that cessation of flutamide resulted in return of HGPIN.[31] Conversely, blockade of 5α-reductase with finasteride appears to have little or no effect on PIN.[32]

Radiation Therapy Eliminates PIN

The prevalence and extent of PIN are decreased after radiation therapy,[33] and PIN retains the features characteristic of untreated PIN. However, 1 study paradoxically noted a higher incidence (70%) of PIN after radiation therapy than expected, but it failed to employ accepted diagnostic criteria for PIN, so its results are not comparable with others.

The long-term efficacy of radiation treatment may depend on eradication of cancer as well as precancerous lesions. The question remains 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–radiation therapy needle biopsies are justified in an attempt to establish the significance of HGPIN 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 cancer recurrence.

Should Men With HGPIN Be Treated?

The clinical importance of recognizing PIN is based on its strong association with prostatic carcinoma, so its identification in biopsy specimens warrants further search for concurrent invasive carcinoma. Follow-up biopsy is suggested at 3- to 6-month intervals for 2 years, and thereafter at 12-month intervals for life.[29,34] If all procedures fail to identify coexistent carcinoma, close surveillance and follow-up are indicated. As HGPIN 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 bacillus Calmette Guérin (BCG), and, in some cases, radical cystectomy.

Most authors agree that the identification of PIN in the prostate should not influence or dictate therapeutic decisions.[35] We are aware of 21 radical prostatectomies that were purposely (3 cases) or inadvertently (18 cases)

performed in patients whose biopsies contained only HGPIN; all but 2 of the cases contained adenocarcinoma in the surgical specimen.

Currently, routine treatment is not available for patients who have HGPIN. Prophylactic radical prostatectomy, radiation, and androgen deprivation are not acceptable treatments for patients who have HGPIN only. The development and identification of acceptable agents to treat HGPIN would fill a therapeutic void. Acapodene, an anti-estrogen, is currently in a phase 2b multicenter, randomized, prospective placebo-controlled human clinical trial to determine if it can treat HGPIN and reduce prostate cancer incidence; preliminary results are encouraging.[36]

PIN offers promise as an intermediate endpoint 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.

Conclusion

HGPIN 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.

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. ■

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Main Points

- Isolated high-grade prostatic intraepithelial neoplasia (HGPIN) is detected in an average of 9% of prostate biopsies. The incidence, extent, and volume of HGPIN increase with patient age; its presence precedes the onset of prostatic carcinoma by 5 to 10 years or more.
- Prostatic intraepithelial neoplasia (PIN), characterized by cellular proliferations within preexisting ducts and acini with cytologic changes mimicking cancer, has been shown to follow 4 main patterns: tufting, micropapillary, cribriform, and flat. These patterns appear to be of diagnostic utility only.
- Immunohistochemical staining for anti-keratin 34ß-E12, the most commonly used staining method for prostatic basal cells, can separate cancer from its mimics. The nuclear marker p63 may be similarly useful, whereas the molecular marker alpha-methylacyl-CoA racemase can separate benign from neoplastic acini.
- With more than 400 genes abnormally expressed in both prostate cancer and HGPIN, the presence of HGPIN cannot be denied as an important marker of potential progression to cancer and cause for close follow-up.
- The transgenic mouse model of prostate cancer has been shown to mimic prostate cancer in humans, including in patterns of metastatic spread, making it and the canine model useful in supporting the role of HGPIN in the continuum to prostate cancer.
- Serum prostate-specific antigen measurement and transrectal ultrasound have not been proved to be able to detect PIN; biopsy remains the definitive method.
- Androgen deprivation therapy has been shown to reduce HGPIN, as has radiation therapy, whereas 5α-reductase therapy has little to no effect.
- Patients with HGPIN should be closely monitored with prostate biopsies at regular intervals for life. Although routine treatment for PIN is not yet available, preliminary results on acapodene, an anti-estrogen, are encouraging.

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