Prostatic intraepithelial neoplasia: a risk factor for prostate cancer

Z. Dovey, MRCP, FRCS,[1] C. M. Corbishley, FRCPath,[2] R. S. Kirby, MD[1]

[1]Cromwell Hospital, London, England
[2]St. George's Hospital, London, England

DOVEY Z, CORBISHLEY CM, KIRBY RS. Prostatic intraepithelial neoplasia: a risk factor for prostate cancer. The Canadian Journal of Urology. 2005;12(Supp 1):49-52.

Prostatic Intraepithelial Neoplasia (PIN) is an increasingly common finding at ultrasound guided prostate biopsy, with the high grade form (HGPIN) thought to be "precancerous". With the more widespread use of extended biopsy protocols, taking sometimes up to 14 cores or more, the incidence of HGPIN can be up to 25%. Histologically, it has many features in common with cancer of the prostate and has been shown to be both associated with cancer at the time of its finding and predictive for the development of prostate cancer in the future. Basic science research has demonstrated genes common specifically to both prostate cancer and HGPIN and immunostaining studies of microvessel density may help to differentiate HGPIN from lower risk PIN. There are no active treatments for HGPIN although there are trials to assess the effectiveness of hormonal therapy and nutritional supplements. Currently most urologists recommend that patients should be followed at 6 monthly intervals with regular PSA and repeat biopsies as indicated.

Key Words: prostatic intraepithelial neoplasia, risk factor

Introduction

Prostatic Intraepithelial Neoplasia (PIN) was formally described in the late 60s by McNeal[1] and later divided into high and low grades.[2] The basic pattern of PIN is characterized microscopically by atypical cellular proliferation within the epithelium of the peripheral ducts and glands of the prostate similar to that seen in carcinoma, but with a preserved basal layer and no evidence of invasion. High Grade PIN (HGPIN) is PIN in its most severe form and tends to show more basal cell layer disruption and proliferation with more extensive nuclear changes. Four specific architectural patterns have been described including tufted, micropapillary, cribriform and flat.[3] See Figures 1 to 4. This pattern recognition is highly observer dependent and mixed types are often seen in the same case. Low grade PIN is now not usually reported by most pathologists. On the basis that all types and grades of PIN form part of a spectrum with normal at one end and preinvasive cancer at the other, the changes of PIN have been described as "precancerous". The clinical picture is more complicated as the natural history of PIN is not well described. There have been conflicting reports of its use as predictor of prostate cancer and there is no clear consensus of the management of PIN once it has been found on prostate biopsy. In this article we aim to review the current literature on PIN, clarify its association with prostate cancer and present a plan for management.

Address correspondence to Professor R. Kirby, Dept. of Uro-Oncology, Cromwell Hospital, Cromwell Road, London, SW5 0TU England

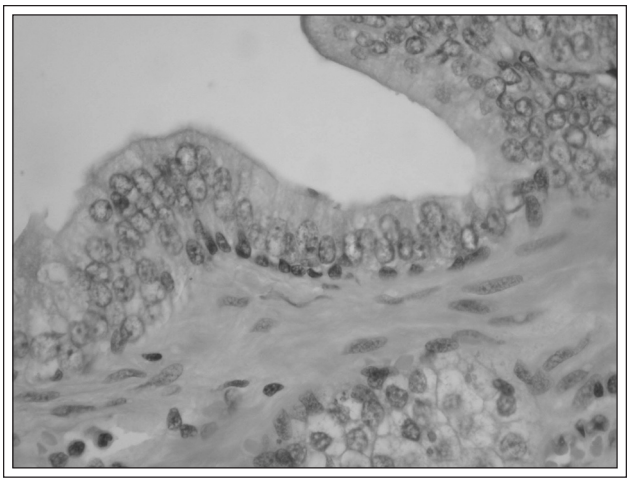

Figure 1. HGPIN flat.

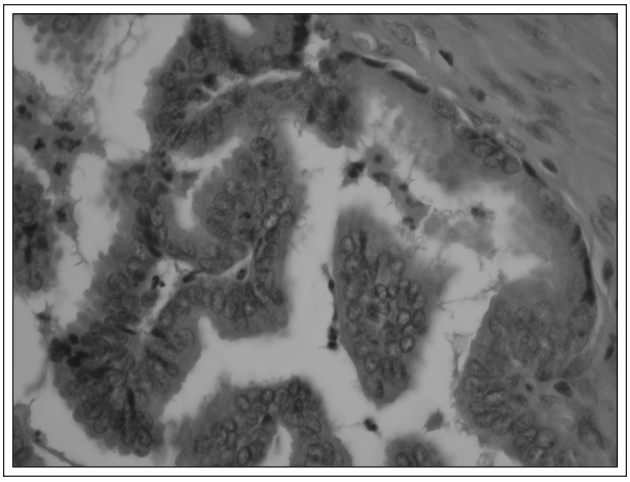

Figure 2. HGPIN micropapillary.

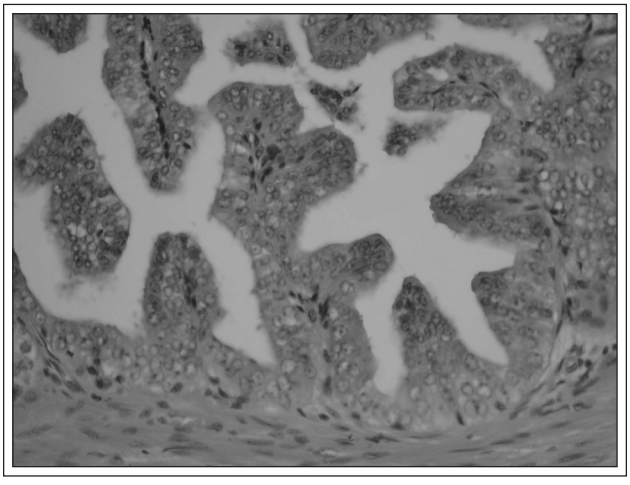

Figure 3. HGPIN tufted.

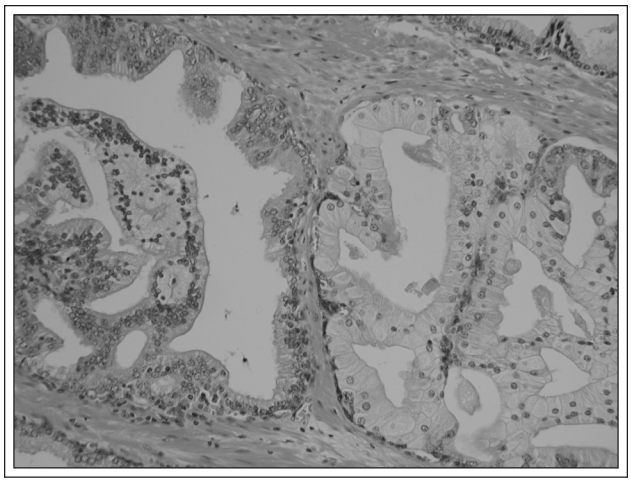

Figure 4. HGPIN cribriform.

Demographics and prostate cancer risk

Widespread use of the extended ultrasound guided fine core biopsy technique has increased the incidence of PIN on biopsy screening programs. Early studies of incidence did not usually differentiate between low and high grade PIN. Using the six core sextant biopsy technique 4.4%–11% of cases were found to have ungraded PIN,[4] whereas HGPIN specifically has been reported in 0.8%–23% of cases.[5] Studying racial variation, Fowler et al[6] found the incidence of HGPIN in black and white men was 13.4% and 5.9% respectively in sextant biopsies. Other studies have shown the advantage of using an extended biopsy technique where 10-12 cores are taken. Rosser et al[7] demonstrated that 47% of their cases with HGPIN were found using an extended biopsy protocol. Overall in patients who present for PSA screening, the incidence of HGPIN may be as high as one in four[8] and, not surprisingly, the more biopsy cores taken, the higher the likelihood of finding HGPIN.

Although the microscopic appearances of high grade PIN are thought to be "precancerous" the natural history of PIN is not clearly established. There have been reports that between 27% and 100% of men with HGPIN detected on six core biopsies will have prostate cancer if a repeat biopsy is performed within 6 months.[9] Much of the early data is based on sextant biopsies and the high incidence of carcinoma in subsequent biopsies is most likely due to biopsy sampling error. Rosser et al[7] reported that extended biopsy protocols (up to 14 cores) within an average of 9 months on patients who had HGPIN on original sextant biopsy revealed cancer in 33% of cases. Borboroglu et al[10] found that 44% of such patients had

prostate cancer on repeat biopsy. The variable pickup rate on second biopsy may be partly explained by inadequate sampling of the peripheral zone in standard sextant biopsies. This is further confirmed by a number of other studies; Presti et al[11] found that sextant biopsy missed 20% of cancers whereas eight core peripheral zone biopsy missed only 5% of cancers; Chen et al[12] found that the sensitivities of sextant and ten core biopsy procedures were 73% and 96% respectively.

Other studies have also confirmed HGPIN is associated with a high risk prostate cancer. Keetch et al[13] showed that repeat biopsy found cancer in 19% of patients with low grade PIN on their original biopsies and 51% of those with HGPIN. These patients were originally biopsied as a part of a screened PSA population and then rebiopsied to follow the intial findings of PIN. More recently, Abdel-Khalak et al[8] showed a cancer detection rate in men with no HGPIN who had a repeat extended biopsy for a rising PSA level was 22% as compared to 36% who had HGPIN on their original biopsy. The probability of detecting cancer on repeat biopsy increases the more cores there are with HGPIN in the original biopsy series,[14] although the position of the cores containing PIN does not necessarily correlate well with the site(s) of tumor foci found in subsequent biopsies. Shepherd et al[15] showed that repeat biopsy only on the side of the HGPIN misses 35% of cancers.

The natural history of HGPIN suggests it is predictive for the development of prostate cancer in the future. Leftkowitz et al[9] studied the development of prostate cancer over a 3 year period with men who had been found to have HGPIN on biopsy and showed that over 25% of men go on to develop cancer. Similarly, San Fransisco et al[16] examined patients with HGPIN on initial biopsy compared to controls with benign histology and followed them up for an average of 34.8 and 36.6 months respectively. Twenty four percent of patients in the HGPIN group developed cancer compared to 2.3% in the control group. Indications for repeat biopsy included two successive increases in PSA level or a change in DRE findings. There was no significant predictive value in the four histological patterns described above.[3]

There are recent reports that contradict the above findings. Postma et al[17] in the Rotterdam Section of the European Randomized Study of Screening for prostate cancer, stated that, after two rounds of screening, that isolated PIN was not predictive for prostate cancer. However both their sets of biopsies were only sextant biopsies and additional cores were only taken on subsequent biopsies from areas previously found to contain HGPIN. Our view is that their biopsy protocol may have been inadequate and would have missed many cases of both HGPIN and prostate cancer.

Clinical observations that PIN is a risk factor and may act as a precursor for prostate cancer are reinforced by basic science research. Ashida et al[18] identified 21 up-regulated genes and 63 down-regulated genes found more commonly in PIN and prostate cancer cells as compared to normal prostate cells. These were considered to be involved in the early stage of prostate carcinogenesis. Common minichromosome maintenance proteins (MCM7) are found more commonly in proliferating epithelial cells of PIN and prostate cancer tissue than in benign hypetrophic prostate tissue.[19] Immunostaining studies using microvessel density may help to distinguish HGPIN from low grade PIN and reactive changes and so differentiate which patients require repeat follow up biopsy in the absence of PSA change.[20]

Management

As a precursor lesion, HGPIN represents a difficult challenge to the urologist. There are ongoing studies to assess chemopreventative strategies, including nutritional supplementation and antiandrogens.[21] There is one published trial assessing the effectiveness of neoadjuvant hormonal therapy which found a significant reduction in the incidence of PIN, but no affect was observed on PSA recurrence at a median follow up of 32 months.[22] There is a risk of missing HGPIN with an associated cancer at the time of the original biopsy therefore subsequent biopsies should use an extended (preferably 12 core) protocol and be performed by an experienced clinician so that all areas of the prostate, particularly the peripheral zone are adequately sampled. Although there is no evidence of a causal relationship between HGPIN and PSA,[21] we suggest that a rising PSA in a patient with known HGPIN may imply a progression to full blown cancer. Radiological investigations have not proven helpful but tissue molecular studies and microvessel density[20] may provide useful information in defining a "subset" of patients with PIN who are more prone to progress to cancer and who should be rebiopsied even in the absence of a change in PSA or DRE findings. Until then, most centres would advocate a policy of regular follow-up with 6 monthly PSA testing, with consideration for rebiopsy based primarily on rate of rise of PSA.[16]

Conclusion

There is now sufficient evidence to suggest that HGPIN is a precursor of prostate cancer and as such is predictive for its' future development. If HGPIN is found at sextant biopsy then early repeat biopsy with an extended protocol should be considered, particularly if radical therapy for carcinoma is contemplated. Otherwise patients should be followed at 6 monthly intervals with regular PSA and repeat biopsies as indicated. Future developments may allow patients with "high risk" PIN to be singled out for repeat biopsy in the absence of a rise in clinical suspicion. Chemopreventative treatments, including hormonal therapy, antiandrogens and nutritional supplements are currently under trial. □

References

1. McNeal JE. Origin and development of carcinoma of the prostate. *Cancer* 1969;23:24-34.
2. McNeal JE, Bostwick DG. Intraductal dysplasia. A premalignant lesion of the prostate. *Hum Path* 1986;17:64-71.
3. Bostwick DG et al. Architectural patterns of high grade prostatic intraepithelial neoplasia. *Hum Path* 1993;24:298-310.
4. Wills ML et al. Incidence of high-grade prostatic intraepithelial neoplasia in sextant needle biopsy specimens. *Urology* 1997;49(3):367-373.
5. Sakar et al. Epidemiology of high grade prostatic intraepithelial neoplasia. *Scand J Urol Nephrol* Suppl 2000;205:11-18.
6. Fowler JE Jr et al. Prospective study of correlations between biopsy-detected high grade prostatic intraepithelial neoplasia, serum prostatic antigen concentration and race. *Cancer* 2001;91:1291-1296.
7. Rosser CJ et al. Detection of high grade prostatic intraepithelial neoplasia with five region biopsy technique. *Urology* 1999;54:853-856.
8. Abdel Khalek M et al. Predictors of prostate cancer on extended biopsy with high grade prostatic intraepithelial neoplasia: a multivariate analysis model. *BJU Int* 2004;94:528-533.
9. Leftkowitz et al. Follow up interval biopsy 3 years after diagnosis of high grade prostatic intraepithelial neoplasia is associated with a high likelihood of prostate cancer, independent of change in prostatic antigen levels. *J of Urol* 2002;168:1415-1418.
10. Borboroglu PG et al. Repeat biopsy strategy in patients with atypical small acinar proliferation or high grade prostatic intraepithelial neoplasia onj initial prostate needle biopsy. *J Urol* 2001;166:866-870.
11. Presti JC Jr et al. The optimal systematic prostate biopsy scheme should include 8 rather than 6 biopsies. Results of a prospective clinical trial. *J Urol* 2000;163:163-167.
12. Chen ME et al. Optimization of prostate biopsy strategy using computer based analysis. *J Urol* 1997;158:2168-2175.
13. Keetch DW et al. Morphometric analysis and clinical follow up of isolated prostatic intraepithelial neoplasia in the needle biopsy of the prostate. *J Urol* 1995;154:347-351.
14. Kronz JD et al. Predicting cancer following a diagnosis of high grade prostatic intraepithelial neoplasia on needle biopsy: data on men with more than one follow up biopsy. *Am J Sur Path* 2001;25:1079-1085.
15. Shepherd et al. Repeat biopsy strategy in men with isolated prostatic intraepithelial neoplasia on prostate needle biopsy. *J Urol* 1996;156:460-463.
16. San Fransisco IF et al. Clinical management of prostatic intraepithelial neoplasia as diagnosed by extended needle biopsies. *BJU Int* 2003;91:350-354.
17. Postma R et al. Lesions predictive for prostate cancer in a screened population : first and second round findings. *The Prostate* 2004;61:260-266.
18. Ashida S et al. Molecular Features of the transition from prostatic intraepithelial neoplasia to prostate cancer: genome wide gene expression profiles of prostate cancers and PINs. *Cancer Res* 2004;64:5963-5972.
19. Padmanabhan V et al. DNA replication regulation protein Mcm7 as a marker of proliferation in prostate cancer. *J Clin Pathol* 2004;57(10):1057-1062.
20. Sinha AA et al. Microveseel density as a molecular marker for identifying high grade prostatic intraepithelial neoplasia precursors to prostate cancer. *Exp Mol Path* 2004;77:153-159.
21. Cheng L et al. Prostatic intraepithelial neoplasia: an update. *Clin Prostate Cancer* 2004;3(1):26-30.
22. Balaji KC et al. Effect of neoadjuvant hormonal therapy on prostatic intraepithelial neoplasia and its prognostic significance. *J Urol* 1999;162:753-757.