CURRENT SIGNIFICANCE OF THE FINDING OF HIGH GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA IN THE PROSTATE BIOPSY

J. Bastarós*, J. Placer, A. Celma, J. Planas, J. Morote

Servicio de Urología y Trasplante Renal, Hospital Vall d’Hebron, Universidad Autónoma de Barcelona, Barcelona, Spain

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Abstract
Introduction: High grade prostatic intraepithelial neoplasia (HGPIN) is regarded as a precursor of prostate cancer (PC). However, its relationship to cancer has changed throughout the literature, being currently poorly defined and remains controversial for urologists in their clinical practice. Because of his frequency and the impact on patient outcomes that the lack of consensus clinical attitude could carry out, it seems advisable to review the understanding of this disease.

Objective: The aim of this literature review is to summarize the main features of this entity (histopathology, molecular, epidemiological) and evaluate their relationship with prostate adenocarcinoma, explaining the variation of incidence seen in the literature and the clinical significance of their finding.

Material and Methods: Review of the literature, based on the research and analysis of publications found in PubMed with the words “prostate” and “intraepithelial neoplasms”.

Results: The HGPIN detection rate has increased to the extent that it has increased the number of punctures in prostate biopsies. With the current biopsy schemes (10–12 punctures), the detection rate of PC in repeat biopsies is similar in patients with and without isolated HGPIN. However, HGPIN multifocality predicts increased risk of PC detection in repeat biopsy.

Conclusion: HGPIN detection is common with current biopsy schemes. Its genetic relationship with PC is clear and its multifocality is the most important predictor factor of PC.

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en su práctica clínica. Puesto que la HGPIN es un hallazgo frecuente en la biopsia prostática y actualmente no existe una actitud clínica consensuada, es recomendable un esfuerzo en la comprensión de su significado clínico.

**Objetivo:** Sintetizar las principales características de la HGPIN y evaluar su relación con el CP. Justificar las variaciones de su incidencia y analizar el significado clínico actual de su detección en la biopsia prostática.

**Material y métodos:** Revisión de la literatura basada en la búsqueda y análisis de las publicaciones halladas en PubMed con las palabras «prostate» e «intraepithelial neoplasms».

**Resultados:** La tasa de detección de HGPIN se ha incrementado en la medida en que se ha aumentado el número de punciones realizadas en la biopsia prostática. Con los esquemas de biopsia actuales (10–12 punciones), la tasa de detección de CP en biopsias de repetición es similar en pacientes con y sin HGPIN aislada. Sin embargo, la multifocalidad de la HGPIN predice un mayor riesgo de detección de CP en la biopsia de repetición.

**Conclusión:** La detección de HGPIN es frecuente con los esquemas actuales de biopsia. Su relación genética con el CP es clara y su multifocalidad es el factor predictor de CP más importante.

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**Background**

The role of prostatic intraepithelial neoplasia (PIN) as a precursor of a number of prostate cancers (PC) was described in the 1960s. Subsequently known as intraductal dysplasia, the current term of PIN was proposed by Bostwick and Brawer in 1987 and was accepted by consensus in 1989.

The term PIN covers morphological changes in which the prostate epithelial cells are present in enlarged glands and are branched with increasing complexity in its inner contours, similar to nonneoplastic glands. The proliferation of this epithelium produces a mottled layer of pseudostratified cells with cytologic atypia similar to those of PC. Unlike PC, the architecture of PIN is normal, and its glands contain basal cells in its periphery. In its original histological description, PIN was subdivided into 3 degrees. PIN was subsequently subclassified into high or low grade, equivalent to grade 1 and 2–3, respectively. Due to the lack of clinical relevance, many authors believe that low-grade PIN should not be reported in pathological reports, although some have recommended labeling borderline cases as high-grade. There are up to 4 architectural patterns for PIN (Fig. 1). The flat pattern consists of a single layer of cells with atypical nuclei. The tufting or quilted pattern, which is the most frequent, alternates between areas of stratification and accumulations of cells adjacent to areas of lesser hyperplasia. When these cell accumulations form high epithelial columns with a typical lack of vascular fibers, it is known as a micropapillary pattern. Finally, the cribriform pattern shows epithelial cell nests that form cylindrical patterns.

Histologically, high-grade PIN (HGPIN) can resemble other entities, some of which are benign (clear cell cribriform hyperplasia, basal cell hyperplasia) and others that have markedly aggressive behavior (cribriform adenocarcinoma, ductal adenocarcinoma, etc.). A common differential diagnosis when there is a reduced group of atypical glands immediately adjacent to an area of HGPIN consists of understanding whether those small glands represent a tangential section of the glandular area of the HGPIN or a focus of carcinoma adjacent to the PIN area. These foci are known as high-grade prostatic intraepithelial neoplasia with adjacent small atypical glands. If these glands show some positivity for basal cell markers, they should be diagnosed as HGPIN.

**Molecular markers of high-grade prostatic intraepithelial neoplasia**

A number of genetic abnormalities present in PC can be found in HGPIN lesions. These abnormalities include the overexpression of alpha-methylacyl coenzyme A reductase (AMACR), loss of p53, phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and retinoblastoma protein, hypermethylation of the promoter region of the glutathione S-transferase p1 gene and fusion of the transmembrane protease serine 2 genes. Ideally, it would be possible to identify specific changes between a benign prostate, HGPIN and PC. However, there are currently no known molecular markers that can provide an appropriate diagnostic classification. The immunohistochemical expression of a number of proteins might have a role in the diagnosis of HGPIN. Immunohistochemical stainings in HGPIN of high molecular weight cytookeratins (detected with the anticytokeratin antibody 34bE12) or p63 demonstrate the presence of basal cells that are absent in PC. Using the combination with triple antibody for AMACR, high molecular weight cytookeratins and p63, HGPIN expresses nuclear p63 and cytoplasmic 34bE12 in the basal cells and AMACR in the cytoplasm of glandular cells, which allows it to be differentiated from benign glands and PC.

A study by Morote et al. published in 2008 analyzed whether the expression of the prostate tumor overexpressed 1 (PTOV-1) gene in HGPIN lesions is associated with the presence of PC. Given that PTOV-1 is overexpressed in HGPIN and PC, the hypothesis was established that PTOV-1 expression in HGPIN isolated in positive biopsies would predict PC in repeated biopsies. The immunohistochemical expression of PTOV was analyzed in 140 patients. Cystoprostatectomy specimens for bladder cancer and radical prostatectomy specimens (both from patients with HGPIN and without PC) were used as negative and positive controls, respectively.
This study revealed that the PTOV-1 overexpression was the only independent predictor of PC in repeated biopsies. A histoscore of 100 was established as a cutoff in PTOV-1 expression in a biopsy with HGPIN; past this point, a rebiopsy should be performed due to the high probability of PC.\(^\text{10}\)

The PCA3 gene is overexpressed in prostate tumor tissue. This overexpression also seems to occur in HGPIN. In a European multicenter study that included patients with an initial negative biopsy, those patients who were diagnosed with PC during the follow-up had significantly increased urinary PCA3 scores after prostate massages. This study found no difference in PCA3 expression in patients with previous diagnoses of HGPIN.\(^\text{11}\) In a subsequent study, our group found that the diagnostic efficacy of urinary PCA3 following prostatic massage was lower in patients with HGPIN.\(^\text{12}\)

It is important to note that if we compare extensive biopsy with the sextant scheme, the detection rate for HGPIN tends to increase.\(^\text{20}\) This variability observed in the literature can be attributed to the absence of uniform diagnostic criteria, nonstandardized histological techniques in the processing of samples, differences in age, ethnicity and family predisposition among the study populations and the disparity in the indication criteria for prostate biopsy.

Sakr et al. analyzed 370 prostate specimens in a population composed of 60% African American males and 40% white males. A greater spread of the lesions was observed in the African American males. When these results were compared with a cohort of 345 men who underwent radical prostatectomy, the authors observed a similar distribution of HGPIN, once the sample was standardized for age and race.\(^\text{21}\)

### Prevalence and incidence of high-grade prostatic intraepithelial neoplasia

The prevalence of HGPIN is high and might well be underestimated, given the fact that its diagnosis is only histological. The reported incidence of HGPIN varies greatly, which could be due to the population studied, the specimen type and the diagnostic criteria used. Based on pathological examinations of prostate glands in a necropsy series\(^\text{13}\) and of cystoprostatectomies for cancer bladder,\(^\text{14-16}\) the prevalence of isolated HGPIN is between 40% and 50%, with both prevalence and volume increasing with age. In contrast, the incidence of HGPIN determined in a series of prostate biopsies in screening studies with PSA varied between 1% and 20%.\(^\text{17,18}\) In patients who underwent transurethral prostate resection, this incidence rate reached 30%.\(^\text{19}\) A meta-analysis that analyzed 87,713 patients in 15 studies with strict diagnostic criteria found an incidence of 4%.\(^\text{19}\)

### Relationship between high-grade prostatic intraepithelial neoplasia and prostate cancer

The relationship between HGPIN and PC was initially established in 1986 by Bostwick et al. Subsequent studies have confirmed the strong association between the 2 conditions. HGPIN tends to be multifocal and more frequent in glands with PC.\(^\text{23}\) It is sometimes possible to observe the transition between the 2 conditions.\(^\text{23-26}\)

The review of a radical prostatectomy series allows us to analyze the close association between HGPIN and PC. The incidence of HGPIN observed in radical prostatectomy specimens varies between 50% and 100%,\(^\text{23-26}\) Troncoso et al.\(^\text{16}\) in a series of 100 radical prostatectomy specimens, observed that all the prostate with incidental PC also contained HGPIN. Similarly, the study by Kim and Yang\(^\text{29}\) performed with a group of patients who underwent cystoprostatectomy,
revealed that all patients with incidental PC had HGPIN, while 60% of the specimens without PC had isolated HGPIN. In this study, the extensive lesions were associated to a greater degree with PC than the focal lesions (65% and 30%, respectively). These data reveal that the HGPIN volume is related to the risk of PC.

At the molecular level, HGPIN and PC share the loss of chromosome 8p and acquisitions in 8q. Other chromosomal deletions that frequently appear in HGPIN and PC are those related to 10q, 16q and 18q and the additions to chromosome 7, 10, 12 and Y. A shortening of telomeres and an increase in the activity of the telomeres are observed in both conditions. The glutathione S-transferase pi 1 protein is hypermethylated in many of the glands with HGPIN in a manner similar to that observed in carcinoma. The p16, p53, Bcl-2, MYC and AMACR genes are overexpressed in both types of lesions, and the NKX3.1 and p27 genes are underexpressed. Approximately 20% of HGPIN lesions contain the fusion of transmembrane protease serine 2 and ERG genes, which are also detected in up to 50% of PC lesions. The 2 entities have a greater rate of apoptosis and proliferation than benign glands.\(^1\)

Currently, it is not possible to monitor an HGPIN focus and determine if there is an infiltrating carcinoma or when the PC develops based on an HGPIN focus, which is evidence that has been gained from the natural history of premalignant lesions in other organs. However, there is evidence that not all PC evolves from an HGPIN lesion. In the majority of prostate glands affected by recently developed PC, there are no HGPIN lesions. Even in prostates where both lesions exist, the HGPIN lesions are adjacent to PC foci in only a third of cases. Is not usual for low-grade PC, especially that which lies in the transitional area, to coexist with HGPIN lesions. In summary, HGPIN appears to be a precursor lesion for many, but not all, intermediate to high-grade peripheral PCs.\(^6\)

**Approach upon detection of high-grade prostatic intraepithelial neoplasia**

Since the start of the 1990s, several studies based on a relatively low number of cases have reported a PC risk of up to 50% in patients with isolated HGPIN. More recent reviews have reported that the risk of PC in repeat biopsies does not exceed 20%. This risk is comparable to that observed in patients with an initial negative biopsy with no diagnosis of HGPIN. Perhaps the most important reason for this pronounced decrease is that current biopsy schemes include a greater number of punctures than standard sextant biopsy.\(^16\) This change to more aggressive biopsy schemes has led to an increased detection of PC in initial biopsies, reducing as well the predictive value of the detection of isolated HGPIN for PC. The relationship between the number of prostate biopsy punctures and the risk of finding PC was illustrated in a series of men with isolated HGPIN in the initial biopsy who underwent a new biopsy in a year.\(^16\) The PC detection rates vary according to the biopsy scheme and are higher when the initial biopsy is conducted with a sextant scheme and the repeat biopsy was extensive. Currently, patients with a diagnosis of HGPIN in an extensive initial biopsy are considered to not require a repeat biopsy within the first year of follow-up, in the absence of other clinical indicators of PC.\(^9,30\)

The importance of the sampling scheme in the biopsy has also been observed in a study by Eskicorapci et al.,\(^31\) in which the risk of PC after an initial sextant biopsy with isolated HGPIN was close to 60%, which was significantly greater than that found in patients with no HGPIN. In contrast, these same authors reported that the risk of PC after an extensive biopsy with isolated HGPIN was only 23%, without demonstrating statistically significant differences when comparing the patients with and without prior HGPIN.\(^31\) The study by Lefkowitz et al.,\(^32\) shed more light on when a rebiopsy is necessary for patients with isolated HGPIN. These authors observed that when isolated HGPIN is diagnosed in an extensive prostate biopsy (more than 12 punctures), the rate of PC detection in an immediate extensive rebiopsy was less than 3%. This observation implies that an extensive biopsy has sufficient negative predictive value to rule out the presence of PC concomitant with isolated HGPIN. The series patients were rebiopsied within 3 years; a 26% increase in the PC detection rate was observed. These data show that approximately one fourth of men with isolated HGPIN will have PC, supporting the hypothesis that HGPIN is a risk factor for the development of PC. It is therefore advisable that men with isolated HGPIN undergo a repeat biopsy within 3 years.\(^31\) In an update on this same patient group, a new prostate biopsy was performed at the 6-year follow-up with the PC detection rate rising to 29%. This finding shows that a delay between 3 and 6 years in performing a rebiopsy does not imply a significant increase in the detection of PC.

The clinical parameters (different measurements of serum PSA, rectal examination and imaging studies) have not helped to identify which patients with isolated HGPIN have an increased risk of PC in successive biopsies. The relationship between HGPIN and serum PSA levels has been the object of several publications, with controversial results. Studies performed in the era of sextant prostate biopsies showed that HGPIN is associated with increased total PSA and a reduction in the percentage of free PSA similar to that observed in patients. These association, however, has not been confirmed in more recent publications.\(^31\) PSA velocity has also been evaluated as a predictor of the evolution of isolated HGPIN. Recently, Loeb et al. demonstrated that patients with isolated HGPIN in whom PC was detected during their follow-up had a higher PSA velocity than patients in whom PC was not detected.\(^34\) The limitation of this study was underdiagnosis resulting from having performed the initial sextant prostate biopsy and the rebiopsy at the 1-year follow-up.

The morphology of HGPIN also does not help predict which patients have an increased risk of PC detected in the repeat biopsy. However, the number of punctures affected by HGPIN does appear to be a predictor of PC risk in repeat biopsies. There are studies that describe how the diagnostic frequency of simultaneous PC or on rebiopsy increases according to the number of cylinders affected by HGPIN.\(^31,35,36\) The relationship between the amount of tissue affected by HGPIN and the diagnosis of PC was observed in a series of 245 patients with isolated HGPIN. In this study, the only predictor of PC was the number of punctures that contained HGPIN.\(^37\) However, Naya et al., in a series of 226 patients with isolated HGPIN, observed that the number of...
cylinders with HGPIN is not related to an increased risk of detecting PC in repeat biopsies.\(^1\) This contradiction could be explained by the different biopsy schemes used in the 2 studies.

Recently, other studies have revealed that molecular findings associated with isolated HGPIN could contribute to predicting the risk of detecting PC. A study that analyzed radical prostatectomy specimens revealed that 56% of HGPIN lesions adjacent to PC foci were overexpressed AMACR, compared with 14% of HGPIN lesions nonadjacent to PC foci.\(^3\) In another study, patients with at least 1 gland with HGPIN positive for AMACR had a 5 times greater risk of PC detection in repeat biopsies than patients with no AMACR expression.\(^5\) Studies are therefore needed to validate the value of the quantitative expression of AMACR in isolated HGPIN lesions to predict the risk of PC. Other immunohistochemical markers, such as PTOV-1, could also be useful for determining which patients with isolated HGPIN have a greater likelihood of PC that can only be diagnosed by a rebiopsy.

Therefore, the presence of isolated HGPIN in a biopsy does not require aggressive follow-up in all cases. The management of men with no evidence of PC in a negative rebiopsy after the detection of isolated HGPIN is also clear. When and how to perform repeat biopsies are questions that currently have no answers. Following a recent literature update, Godoy and Taneja\(^17\) proposed that an immediate extensive rebiopsy should be performed in cases of isolated HGPIN detected in a biopsy performed with less than 10 punctures. For patients with isolated HGPIN, identified in a biopsy with an appropriate number of punctures, a repeat biopsy is only advised if serum PSA levels are greater than 10 ng/mL or if there is high clinical suspicion. For men with isolated HGPIN with none of the previous characteristics, follow-up is recommended, PSA measurements every 6 months and a new biopsy at the 3-year follow-up. For men with high PSA velocities >0.75 ng/mL/year or PSA levels >10 ng/mL, the repeat biopsy can be scheduled earlier. To date, this appears to be the most recommended approach for the follow-up of patients with isolated HGPIN, while we await new studies that allow us to add other predictors.

Conclusion

The HGPIN lesion is a precursor entity of PC that should be considered when the lesion is detected in isolation in a prostate biopsy. Although its natural history is not entirely clear, the follow-up of these patients is required, with periodic measurements of serum PSA levels and repeat extensive biopsies in 1 to 3 years, depending on the biopsy scheme employed, the number of punctures affected by HGPIN and the PSA velocity during follow-up. Nevertheless, the lack of molecular markers to enable us to individualize the follow-up of these patients is acknowledged.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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