Prostate adenocarcinoma detected after high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation

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OBJECTIVE

To review specific histological variables in patients with prostate cancer who previously had diagnoses of high-grade prostatic intraepithelial neoplasia (HGPIN) and/or atypical small acinar proliferation (ASAP), compared with those who had no such diagnoses.

PATIENTS AND METHODS

The histological characteristics of prostate cancers which were detected after a previous diagnosis of HGPIN and/or ASAP during 1998–2005 were investigated and correlated with the biopsies from patients with prostate cancer but with no such previous diagnoses.

RESULTS

HGPIN was followed by prostate cancer on repeat biopsy in 16.8% of patients, and ASAP in 26.7%. The mean age of patients with HGPIN or ASAP was higher than in those with no such diagnoses ($P < 0.001$). Similarly, patients with these previous diagnoses had a lower Gleason score ($P = 0.017$ and <0.001, respectively) and lower tumour volume variables (fewer tumour foci, $P = 0.033$ and 0.041, respectively) and shorter cancer ($P = 0.048$ and 0.030) in core biopsies than those without.

CONCLUSIONS

Patients with prostate cancer who had previous biopsies with HGPIN or ASAP were older and has lower grade- and volume-cancers than those who had not.

KEYWORDS

prostate cancer, high-grade prostatic intraepithelial neoplasia, atypical small acinar proliferation, Gleason score, tumour volume

INTRODUCTION

High-grade prostatic intraepithelial neoplasia (HGPIN) has been traditionally considered as a precursor of prostate cancer [1,2] and many studies have addressed this issue. However, recent reports showed a varied association between HGPIN and prostate cancer, at 22–100% [3–9]. Apart from the generic recommendation to repeat the biopsy in these patients, there are no unifying criteria about how and when to do so, and urologists do not agree on the best clinical follow-up strategy in these cases. In addition, some contradictory data were reported relating the potential risk of future prostate cancer with the amount of HGPIN found in the core biopsy [3,8,10–12].

The diagnosis of atypical small acinar proliferation (ASAP) has also been correlated with the finding of prostate cancer in subsequent biopsies [13–17]. Indeed, the term was coined to focus attention in cases not completely fulfilling the minimal criteria of prostate cancer [18], thus advising a close follow-up. Also, there are various reported rates and opinions of the association between ASAP and subsequent prostate cancer [13–17].

Despite the relationship of HGPIN and ASAP with prostate cancer, there is no study comparing the histological characteristics of prostate cancer with and with no previous diagnoses of HGPIN/ASAP. The aim of the present study was to investigate whether these two groups of prostate cancer are different and if so, in what sense.

PATIENTS AND METHODS

All the transrectal core biopsies of the prostate taken from patients at the author's institution during an 8-year period (1998–2005) were included in the analysis. The author conducted or reviewed the histopathological diagnoses in all patients and assessed the recorded data retrospectively. After local anaesthesia, the patients were biopsied under TRUS guidance, using routine methods. Patients with a diagnosis of cancer were treated by following the Institution's protocol [19] and those with a diagnosis of HGPIN or ASAP were followed with a DRE and serum PSA determinations every 6 months. ASAP was diagnosed by strictly applying the histological criteria; consequently, men with large atypical glands were not included in the study. Following precise clinical criteria, including an abnormal DRE and/or abnormal PSA density (>15 ng/mL per mL) or velocity (>0.75 ng/mL/year or >20%/year), patients were advised to have a repeat biopsy.

Six to eight cores of prostate tissue were obtained in every case in the first biopsy, and 10–12 in the subsequent ones, following previously established protocols [5,8,13,20]. Specimens were fixed in formalin and processed routinely. In all, 24–36 consecutive

Variable	Mean (range)	ρ value	P
HGPIN			
Repeat biopsies	1.3 (1–4)		
Gleason score		0.178	0.011
<7	15		
3 + 4	4		
4 + 3	1		
>7	0		
Tumour foci	1.8 (1–4)	0.219	0.003
Length of cancer, mm	5.5 (1–19)	0.213	<0.001
Bilateral tumour invasion		0.139	0.024
Perineural invasion		0.174	0.015
ASAP			
Repeat biopsies	0.8 (1–3)		
Gleason score		0.140	0.022
<7	9		
3 + 4	2		
4 + 3	0		
>7	1		
Tumour foci	2.1 (1–5)	0.232	0.015
Length of cancer, mm	5 (1–14)	0.250	0.005

TABLE 1
The histological findings in prostate cancer with a previous diagnosis of HGPIN or ASAP

histological sections, stained with haematoxylin and eosin, were assessed in every case. HGPIN and ASAP diagnoses were based on previously described criteria [21,22].

Immunostaining with α-methylacyl CoA racemase (p504S, dilution 1 : 100), p63 (1 : 50), and cytokeratin 5.6 (1 : 50, all from Dako, Carpinteria, CA, USA) was used to differentiate, when needed, the diagnostic dilemma between ASAP and minimal cancer [18], or HGPIN and intraductal carcinoma [23].

The presence of HGPIN/ASAP in core biopsies was correlated with several histological variables of prognostic significance in prostate cancer, e.g. bilateral tumour extension, Gleason score, number of tumour foci, total length of cancer measured, as previously stated [19], perineural invasion, vascular permeation, extraprostatic extension, hyaline micronodules, and glomerulation. The time elapsed between the diagnosis of HGPIN or ASAP and that of prostate cancer was also quantified in every patient.

In addition, several histological variables were compared between cancers with previous diagnoses of HGPIN/ASAP and those without, to determine whether there was any significant difference among these two groups of prostate cancer.

RESULTS

Among the 4770 prostate biopsies taken 1450 (30.3%) were diagnosed as prostate adenocarcinoma, 125 (2.6%) as HGPIN and 45 as ASAP (0.9%). Among patients with HGPIN 21 (16.8%) had a diagnosis of cancer in subsequent biopsies, and among ASAP, 12 (26.7%) had so.

The mean (range) age of patients with cancer after HGPIN was 72 (65–81) years, the mean delay between the diagnosis of HGPIN and that of cancer was 12.3 (2–39) months and the number of repeat biopsies needed to diagnose cancer was 1.3 (1–4). Following clinical criteria, no additional biopsies were taken in 29 patients (23.2%). HGPIN continued to be the only finding in repeated biopsies in nine patients (7%).

Table 1 summarizes the pathological findings in prostate cancers diagnosed after HGPIN; notably, 1.4% of prostate cancers diagnosed in this series had one or more previous biopsies in which HGPIN was the unique relevant finding. The Gleason score distribution in these patients was <7 in 15, 3 + 4 in four, 4 + 3 in one and >7 in none. Tumour volume, expressed as the mean (range) number of tumour foci and total length of cancer, was 1.8 (1–4) and 5.5 (1–19) mm, respectively.

There was a correlation between HGPIN in the first biopsy and several histological findings with prognostic significance in subsequent biopsies. Thus HGPIN correlated (Spearman's ρ) with bilateral tumour invasion ($P = 0.024$), Gleason score ($P = 0.011$), number of tumour foci ($P = 0.003$), total length of cancer ($P < 0.001$) and perineural invasion ($P = 0.015$).

When comparing cancers with and with no previous diagnosis of HGPIN, the mean age was significantly higher in the group with previous HGPIN, at 72 (65–81) vs 64.8 (43–77) years ($P < 0.001$); the Gleason score was lower ($P = 0.017$), there were fewer tumour foci, at 1.8 (1–4) vs 2.5 (1–7) ($P = 0.033$), and the total length of cancer less, at 5.5 (1–19) vs 9.7 (1–58) ($P = 0.048$) in the group with previous HGPIN.

The mean age of patients with cancer after a diagnosis of ASAP was 68 (54–87) years, with a delay between diagnosis of ASAP and that of cancer of 12.7 (2–30) months, and 0.8 (1–3) repeat biopsies necessary to diagnose cancer. There was no patient with two consecutive diagnoses of ASAP. Table 1 also summarizes the pathological findings in prostate cancers diagnosed after ASAP; 0.8% of prostate cancers diagnosed had a previous diagnosis of ASAP. The Gleason score distribution in these cases was <7 in nine, 3 + 4 in two, 4 + 3 in none and >7 in one. The tumour volume (number of tumour foci and total length of cancer) was 2.1 (1–5) and 5 (1–14) mm, respectively.

There was a correlation between ASAP in the first biopsy and several histological findings with prognostic significance in subsequent biopsies; ASAP correlated (Spearman's ρ) with Gleason score ($P = 0.022$), number of tumour foci ($P = 0.015$) and total length of cancer ($P = 0.005$).

Comparing patients with cancer with and with no previous ASAP, the mean age was significantly higher in the group with previous ASAP, at 70 (57–79) vs 64.8 (43–77) years ($P < 0.001$), the Gleason score was lower ($P < 0.001$), there were fewer tumour foci, at 2.1 (1–5) vs 2.5 (1–7) ($P = 0.041$) and the total length of cancer lower, at 5 (1–14) vs 9.7 (1–58) mm ($P = 0.030$) in the group with previous ASAP. Two patients had HGPIN and ASAP in the same core, and both had prostate cancer in the subsequent biopsy.

DISCUSSION

In 1987, Bostwick and Brawer [24] used the term PIN to encompass all the previous attempts to define prostate cancer precursors and *in situ* neoplasia. Two decades later there are many reports dealing with the diagnosis and clinical significance of this condition. Despite the diagnostic histological criteria of PIN being well established [21,22] there are considerable differences in reporting it [25].

Currently there is no doubt that HGPIN and prostate cancer are closely related, but there are many questions that remain unsolved and under debate, i.e. to what extent are HGPIN and prostate cancer related? What is the real significance of finding a focus of HGPIN in a core biopsy? How many possibilities are there for detecting prostate cancer after a diagnosis of HGPIN? Is the amount of HGPIN in a core biopsy important from the clinical viewpoint? What must be the urologist's attitude after a diagnosis of HGPIN?

Recent reports on this topic show diverse and sometimes conflicting results [3,8,10–12], e.g. while Bishara *et al.* [3] and Herawi *et al.* [5] found cancer after HGPIN in a repeat biopsy in 28.8% and 30.5% of their cases, respectively, Roscigno *et al.* [8] did so in 45% and Zlotta *et al.* [9] in 100%. Others [6,20,26,27] found it less frequently, in ≈22% of cases, and still others [10] state that the possibility of finding cancer after a biopsy with HGPIN is smaller than after a negative biopsy. This last finding agrees with the present results and seriously questions both the supposed importance of detecting HGPIN for predicting cancer, and the convenience of a repeat biopsy in these patients. However, Goeman *et al.* [28] found a higher risk of discovering cancer on repeat biopsy in cases with low-grade rather than with HGPIN, thus adding intriguing results to the topic and questioning the presumed irrelevance of a discovery of low-grade PIN.

The influence of the number of HGPIN foci on the probability of finding prostate cancer in a repeat biopsy is also controversial. Roscigno *et al.* [8] detected a higher probability in cases of multifocal HGPIN, while Naya *et al.* [12] suggested that the number of cores affected by HGPIN did not increases the probability of finding cancer in subsequent biopsies.

Once the decision for a repeat biopsy is taken by the urologist, there is no total agreement on when and how to do so. Some [21] recommend taking it within the first 6 months after a diagnosis of HGPIN, while others [8] accept longer periods, even up to 18 months. In the opinion of Epstein [29], currently there is no need to repeat the biopsy within the first year after the diagnosis. In this sense, monitoring the development of serum PSA levels might be the clue for a repeat biopsy. However, Lefkowitz *et al.* [30] found that a high proportion of patients with a diagnosis of HGPIN develop prostate cancer in the following 3 years, regardless of the change in PSA level, and suggest repeating the biopsy in any case. Finally, Kamoi *et al.* [20] advised ipsilateral biopsies, while others [7,8] suggested bilateral, sextant, or even extended 12-core biopsy, because they found prostate cancer in a repeat biopsy on the contralateral side to the previous HGPIN.

There is no previous study comparing the histology of cancer detected after HGPIN with those detected without this antecedent. In the present study, prostate cancers appearing after HGPIN in older patients had lower Gleason scores and smaller tumour volumes.

The term ASAP was coined to resolve the diagnostic dilemma of groups of small prostate glands 'suspicious but not diagnostic' of malignancy. The term immediately gained general acceptance [31,32] and its distinction from so-called 'minimal cancer' was thoroughly analysed [18]. Despite a close relationship of this finding with cancer, controversies remain even between experts [25], most probably reflecting interobserver variations.

ASAP is possibly more closely related to cancer than HGPIN [33,34] and the present results confirm that. The reported mean cancer detection rate in repeated biopsies for ASAP is ≈40% [13–17]. The probability for having cancer after a diagnosis of ASAP is, according to Brausi *et al.* [35], so high that radical prostatectomy might eventually be the elected treatment for these patients. The most extensive opinion favours repeat biopsy [14,16], adding to the sextant strategy with a specific biopsy of the transition zone [13].

Iczkowski *et al.* [15] showed that patients with cancers detected after ASAP and cancer found in the initial biopsy were of similar age and serum PSA level, and Mallen *et al.* [16] reported similar conclusions between patients with ASAP and those with a negative biopsy. Others [36] consider that a diagnostic delay of cancer diagnosis after ASAP well beyond 6 months does not influence the clinical course of these cancers. Finally, there is a higher probability of finding cancer in the repeat biopsy when HGPIN and ASAP coexist in the same core biopsy [15,37].

To date there is no published comparison between the histological characteristics of cancers diagnosed after a diagnosis of ASAP and cancers without this antecedent. As with HGPIN, patients with cancer after ASAP were older, and the tumours had a lower Gleason score and fewer tumour foci.

Obviously, finding prostate cancer in a core biopsy is a combined matter of statistical probabilities and tumour size. There is no definite explanation of why prostate cancer detected after a diagnosis of either HGPIN or ASAP is of lower Gleason score and smaller tumour volume, and there is no previously published reference to this. However, clinically insignificant or small-volume prostate carcinomas have less chance of being sampled in core biopsies than the remaining tumours, and in the particular setting of a 'no tumour present' biopsy in a patient with highly suggestive clinical data, the pathologist might unconsciously assess the submitted material more closely to find, if not cancer, at least some cancer-related features like HGPIN or ASAP.

To summarize, the incidence of HGPIN and ASAP in the present series was 2.6% and 0.9%, with a subsequent cancer rate of 16.8% and 26.7%, respectively, in those who had repeat biopsies. These values agree with those reported previously and further support the relationship between both conditions and cancer. As previously reported, ASAP has a closer relation with cancer than HGPIN. Finally, prostate carcinomas detected after HGPIN or ASAP appear in older patients, are of lower grade, and have a smaller tumour volume than cancers without these antecedents. These differences between prostate cancers with and without previous diagnoses of HGPIN or ASAP have not been reported to date.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Oyasu R, Bahnson RR, Nowels K, Garnett JE.** Cytological atypia in the prostate gland: frequency, distribution, and possible relevance to carcinoma. *J Urol* 1986; **135**: 959–62

2 **Sakr WA, Grignon DJ, Haas GP *et al.*** Epidemiology of high-grade prostatic intraepithelial neoplasia. *Pathol Res Pract* 1995; **191**: 838–41

3 **Bishara T, Ramnani DM, Epstein JI.** High-grade prostatic intraepithelial neoplasia on needle biopsy: risk of cancer on repeat biopsy related to number of involved cores and morphological pattern. *Am J Surg Pathol* 2004; **28**: 629–33

4 **Davidson D, Bostwick DG, Qian J *et al.*** Prostatic intraepithelial neoplasia is a risk factor for adenocarcinoma: predictive accuracy in needle biopsies. *J Urol* 1995; **154**: 1295–9

5 **Herawi M, Kahane H, Cavallo C, Epstein JI.** Risk of prostate cancer on re-biopsy following a diagnosis of high-grade prostatic intraepithelial neoplasia (HGPIN) is related to the number of cores sampled. *J Urol* 2006; **175**: 121–4

6 **Langer JE, Rovner ES, Coleman BG *et al.*** Strategy for repeat biopsy of patients with prostatic intraepithelial neoplasia detected by prostate needle biopsy. *J Urol* 1996; **155**: 228–31

7 **Netto GJ, Epstein JI.** Widespread high-grade prostatic intraepithelial neoplasia on prostatic needle biopsy: a significant likelihood of subsequently diagnosed adenocarcinoma. *Am J Surg Pathol* 2006; **30**: 1184–8

8 **Roscigno M, Scattoni V, Freschi M *et al.*** Monofocal and plurifocal high-grade prostatic intraepithelial neoplasia on extended prostate biopsies: factors predicting cancer detection on extended repeat biopsy. *Urology* 2004; **63**: 1105–10

9 **Zlotta AR, Raviv G, Schulman CC.** Clinical prognostic criteria for later diagnosis of prostate carcinoma in patients with initial isolated prostatic intraepithelial neoplasia. *Eur Urol* 1996; **30**: 249–55

10 **Gokden N, Roehl KA, Catalona WJ, Humphrey PA.** High-grade prostatic intraepithelial neoplasia in needle biopsy as risk factor for detection of adenocarcinoma: current level of risk in screening population. *Urology* 2005; **65**: 538–42

11 **Kronz JD, Allan CH, Shaikh AA, Epstein JI.** 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 Surg Pathol* 2001; **25**: 1079–85

12 **Naya Y, Ayala AG, Tamboli P, Babaian RJ.** Can the number of cores with high-grade prostatic intraepithelial neoplasia predict cancer in men who undergo repeat biopsy? *Urology* 2004; **63**: 503–8

13 **Borboroglu PG, Sur RL, Roberts JL, Amling CL.** Repeat biopsy strategy in patients with atypical small acinar proliferation or high grade prostatic intraepithelial neoplasia on initial prostate needle biopsy. *J Urol* 2001; **166**: 866–70

14 **Epstein JI, Herawi M.** Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. *J Urol* 2006; **175**: 820–4

15 **Iczkowski KA, Chen HM, Yang XJ, Beach RA.** Prostate cancer diagnosed after initial biopsy with atypical small acinar proliferation suspicious for malignancy is similar to cancer found on initial biopsy. *Urology* 2002; **60**: 851–4

16 **Mallen E, Gil P, Sancho C *et al.*** Atypical small acinar proliferation. Review of a series of 64 patients. *Scand J Urol Nephrol* 2006; **40**: 272–5

17 **Scattoni V, Roscigno M, Freschi M *et al.*** Predictors of prostate cancer after initial diagnosis of atypical small acinar proliferation at 10–12 core biopsies. *Urology* 2005; **66**: 1043–7

18 **Iczkowski KA, Bostwick DG.** Criteria for biopsy diagnosis of minimal volume prostatic adenocarcinoma: analytic comparisosn with non-diagnostic but suspicious atypical small acinar proliferation. *Arch Pathol Laboratory Med* 2000; **124**: 98–107

19 **Lopez JI, Etxezarraga C.** The combination of millimetres of cancer and Gleason Index in core biopsy is a predictor of extraprostatic disease. *Histopathology* 2006; **48**: 663–7

20 **Kamoi K, Troncoso P, Babaian RJ.** Strategy for repeat biopsy in patients with high grade prostatic intraepithelial neoplasia. *J Urol* 2000; **163**: 819–23

21 **Argani P, Epstein JI.** Inverted (hobnail) high-grade prostatic intraepithelial neoplasia (PIN). report of 15 cases of a previously undescribed pattern of high-grade PIN. *Am J Surg Pathol* 2001; **25**: 1534–9

22 **Young RH, Srigley JR, Amin MB, Ulbright TM, Cubilla AL.** Tumors of the prostate gland, seminal vesicles, male urethra, and penis. *Atlas of Tumor Pathology*, Third Series, Fascicle 28, Washington DC: AFIP, 2000: 69–109

23 **Guo CC, Epstein JI.** Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance. *Mod Pathol* 2006; **19**: 1528–35

24 **Bostwick DJ, Brawer MK.** Prostatic intra-epithelial neoplasia and early invasion in prostate cancer. *Cancer* 1987; **59**: 788–94

25 **Egevad L, Allsbrook WC, Epstein JI.** Current practice of diagnosis and reporting of prostatic intraepithelial neoplasia and glandular atypia among genitourinary pathologists. *Mod Pathol* 2006; **19**: 180–5

26 **O'dowd GJ, Miller MC, Orozco R, Veltri RW.** Analysis of repeated biopsy results within 1 year after a non cancer diagnosis. *Urology* 2000; **55**: 553–9

27 **Tan PH, Tan HW, Tan Y, Lim CN, Cheng C, Epstein JI.** Is high-grade prostatic intraepithelial neoplasia on needle biopsy different in an Asian population: a clinicopathologic study performed in Singapore. *Urology* 2006; **68**: 800–3

28 **Goeman L, Joniau S, Ponette D *et al.*** Is low-grade prostatic intraepithelial neoplasia a risk factor for cancer? *Prostate Cancer Prostatic Dis* 2003; **6**: 305–10

29 **Epstein JI.** What's new in prostate cancer disease assessment in 2006? *Curr Opin Urol* 2006; **16**: 146–51

30 **Lefkowitz GK, Taneja SS, Brown J, Melamed J, Lepor H.** Follow-up interval prostate biopsy 3 years after diagnosis of high grade prostatic intraepithelial neoplasia is associated with high likelihood of prostate cancer, independent of change in prostate specific antigen levels. *J Urol* 2002; **168**: 1415–8

31 **Samaratunga H, Gardiner RA, Yaxley J, Brown I.** Atypical prostatic glandular

proliferation on needle biopsy: Diagnostic implications, use of immunohistochemistry, and clinical significance. *Anal Quant Cytol Histol* 2006; **28**: 104–10

32 **Montironi R, Scattoni V, Mazzucchelli R, Lopez-Beltran A, Bostwick DG, Montorsi F.** Atypical foci suspicious but not diagnostic of malignancy in prostate needle biopsies (also referred to as "atypical acinar proliferation suspicious for but not diagnostic of malignancy). *Eur Urol* 2006; **50**: 66–74

33 **Moore CK, Karikehalli S, Nazeer T, Fisher HA, Kaufman RP Jr, Mian BM.** Prognostic significance of high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation in the contemporary area. *J Urol* 2005; **173**: 70–2

34 **Ouyang RC, Kenwright DN, Nacey JN, Delahunt B.** The presence of atypical small acinar proliferation in prostate needle biopsy is predictive of carcinoma on subsequent biopsy. *BJU Int* 2001; **87**: 70–4

35 **Brausi M, Castagnetti G, Dotti A, De Luca G, Olmi R, Cesinaro AM.** Immediate radical prostatectomy in patients with atypical small acinar proliferation. Over treatment? *J Urol* 2004; **172**: 906–8

36 **Fadare O, Wang S, Mariappan MR.** Practice patterns of clinicians following isolated diagnoses of atypical small acinar proliferation on prostate biopsy specimens. *Arch Pathol Laboratory Med* 2004; **128**: 557–60

37 **Schlesinger C, Bostwick DG, Iczkowski KA.** High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation: predictive value for cancer in current practice. *Am J Surg Pathol* 2005; **29**: 1201–7

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Abbreviations: **(HG)PIN**, (high-grade) prostatic intraepithelial neoplasia; **ASAP**, atypical small acinar proliferation.