

PREVALENCE OF HIGH-GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA AND ITS RELATIONSHIP TO SERUM PROSTATE SPECIFIC ANTIGEN

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ABSTRACT

Objective: We assessed the incidence of high-grade prostatic intraepithelial neoplasia (HGPIN) in prostates removed for bladder cancer, and evaluated its correlation with preoperative serum prostate specific antigen (PSA).

Materials and Methods: We reviewed the histology of the prostate from men who underwent cystoprostatectomy for bladder cancer without known prostate pathology prior to surgery. Preoperative serum PSA levels in patients with HGPIN were analyzed.

Results: 61 cystoprostatectomy specimens from May 1992 to April 1999 were reviewed. High-grade prostatic intraepithelial neoplasia (PIN) was found in 46/61 (75%) of the prostate specimens, including 21/21 (100%) patients with prostatic cancer, and 25/40 (63%) patients without prostatic cancer. The mean serum PSA in men with PIN without evidence of prostatic adenocarcinoma was 1.9 ng/mL (SD=2.026).

Conclusion: The incidence of isolated high-grade PIN was 63%. The presence of high-grade PIN does not result in a significant elevation of serum PSA.

Key words: prostate; pathology; prostate-specific antigen; prostatic intraepithelial neoplasia; prevalence
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INTRODUCTION

Prostatic intraepithelial neoplasia (PIN) is defined by neoplastic growth of epithelial cells within preexisting benign prostatic acini or ducts. High-grade PIN is considered a premalignant lesion (1,2) and the development of high-grade PIN may precede the onset of prostatic adenocarcinoma by more than ten years (3). PIN is frequently seen in association with prostatic adenocarcinoma (1). Thus, the finding of isolated high-grade PIN on a needle core biopsy is generally accepted as an indication to repeat biopsy (4-6).

The correlation between prostatic adenocarcinoma and serum PSA has been extensively studied. However, only a few studies have focused on the relationship between PIN and PSA. Some studies

suggest that PIN causes serum PSA elevation (7), while other studies dispute this relationship (8,9). To most directly assess the relationship between PIN and PSA, PSA levels can be correlated with the finding of isolated PIN, where the presence of adenocarcinoma has been excluded by an examination of the entire prostate specimen. Previous studies have been based on either prostate biopsy tissue, which is subject to sampling error, or radical prostatectomy specimens, which contain adenocarcinoma. However, the present study is based on an examination of the complete prostate obtained during cystoprostatectomy in men with urothelial carcinoma. We assessed the effect of high-grade PIN on serum PSA by evaluating the preoperative PSA in men with high-grade PIN without any evidence of prostatic adenocarcinoma (isolated high-grade PIN).

MATERIALS AND METHODS

Using a database at the University of Chicago, Department of Pathology, 61 men who underwent cystoprostatectomy for urothelial carcinoma of the bladder between May 1992 and April 1999 were identified. None of the patients had a known history of prostate pathology prior to surgery. At the time of surgery, all specimens were fixed in formalin within one hour of surgery. The prostates were serially sectioned at 4mm intervals. The histology of the prostate was reviewed and specifically assessed for the presence of PIN and adenocarcinoma of the prostate by a single pathologist (XJY) with expertise in prostate pathology.

Criteria for defining high-grade PIN included (1) epithelial cell proliferation within the ducts and acini, forming pseudostratified layers, (2) enlargement, elongation, irregularity and hyperchromasia of the nuclei, and (3) multiple prominent nucleoli. High-grade PIN was classified as "focal" if there were three or fewer separate foci/acini of high-grade PIN, and as "extensive" if there were more than three foci/acini of high-grade PIN on different sections. Adenocarcinomas were graded using the Gleason system. Pre-operative serum PSA, obtained within 1.5 years prior to surgery, was available for 34 patients. Chi-square analysis and logistic regression analysis were performed using computer software, Minitab Release 12.

RESULTS

The mean age of the patients was 69 years. High-grade PIN was found in 46/61 (75%) prostates examined. The high-grade PIN was noted in 21/21 (100%) patients who had prostatic adenocarcinoma and in 25/40 (63%) patients who had no evidence of prostatic adenocarcinoma. PIN was considered focal in 26/61 (43%), and extensive in 20/61 (33%) patients. Of the patients with focal PIN, 8/26 (31%) had prostatic adenocarcinoma, and of the patients with extensive PIN, 13/20 (65%) had prostatic adenocarcinoma ($p=0.021$). The majority (95%) of patients with prostatic adenocarcinomas had tumors categorized as Gleason score six or less. The mean PSA in 21 men with isolated high-grade PIN (without prostatic adenocarcinoma) was 1.9 ng/mL (Range 0.7-8

ng/mL; SD=2.03). The serum PSA levels did not correlate with the categorization of PIN as focal or extensive ($p=0.485$).

DISCUSSION

In our study, high-grade PIN was seen in 75% of all prostates examined, and in 63% of prostates without associated prostatic adenocarcinoma. The true prevalence of PIN and adenocarcinoma may be even higher, since any review of pathologic specimens is subject to sampling error. None of the patients without high-grade PIN had evidence of prostatic adenocarcinoma. To determine the prevalence of PIN in the general population, other investigators have examined prostate specimens obtained from needle biopsies, transurethral resections (TUR), autopsies, or radical prostatectomy specimens removed for treatment of prostate cancer (Table-1). The incidence of isolated high-grade PIN on needle biopsy was reported to be from 0.7% to 20% (10). Needle core biopsies sample less than 1% of the total prostate volume and, therefore, sampling error is inherent to the procedure. The frequency of isolated high-grade PIN found in tissues obtained from transurethral resection of the prostate ranges from 2.8% to 3.2% (11,12). However, most of the prostate tissue removed during a TUR is from the transition zone, while PIN is most frequently found in the peripheral zone.

Studies based on examination of the entire prostate identified a higher frequency of isolated PIN. In a review of autopsy specimens from men over the age of 50 years, McNeal and Bostwick found PIN in 82% of men with prostatic adenocarcinoma, and 43%

Table 1 - Incidence of isolated high-grade prostatic intraepithelial neoplasia (HGPIN).

Specimens	Isolated HGPIN
Prostate needle biopsy (10)	0.7 to 20%
Transurethral resection (11,12)	2.8 to 3.2%
Autopsy prostate (1,3,13,14)	38 to 46%
Cystoprostatectomy (15-17)	10 to 72%

of men with benign prostates (1). In other studies based on prostates obtained at autopsy, the incidence of high-grade PIN ranged from 38%-46% (3,13,14). Other studies using cystoprostatectomy specimens have reported incidences of isolated high-grade PIN ranging from 10 to 72% (Table-2) (15-17). The lower incidence of high-grade PIN reported in studies based on cystoprostatectomy specimens when compared to studies based on autopsy findings, may be related to differences in patient populations, sampling methods, or diagnostic criteria applied by the pathologists. In our study, isolated high-grade PIN was seen in 63% of the cystoprostatectomy specimens, and this is consistent with a recent report by Troncoso et al. (17). Troncoso et al. reported that the incidence of high-grade PIN in patients with prostate cancer was 100% (61/61), and the incidence of isolated high-grade PIN was 72% (28/39).

Therefore, isolated high-grade PIN is not an uncommon finding. With this present study included, there are at least four studies assessing the incidence of PIN in cystoprostatectomy specimens. The combined incidence in these studies of high-grade PIN found in association with prostate cancer is 52% (75/143), while the incidence of isolated high-grade PIN is 48% (68/143) (Table-2). Although the finding of high-grade PIN on prostate needle biopsy has been considered an indication to repeat biopsy, the cystoprostatectomy results underscore the fact that nearly half of all patients with high-grade PIN may not have associated adenocarcinoma.

PSA is produced by both benign and malignant epithelial cells of the prostate. It is well documented that the presence of prostatic adenocarcinoma can cause

elevation of serum PSA. The mechanism by which PSA is released into the serum is not completely understood. It may be related to the disruption of the basement membrane caused by tumor invasion or other destructive processes, such as inflammation or infarct. The basement membrane within PIN is intact. Therefore, it is reasonable to believe that PSA produced by neoplastic cells in PIN is not released into the serum at clinically significant levels. Our study provides direct evidence that PIN does not result in a significant elevation of serum PSA. Isolated PIN was not associated with an elevated serum PSA and the serum PSA did not correlate with the extent of PIN found in the prostate.

Previous studies assessing the relationship between high-grade PIN and serum PSA have reached conflicting conclusions. In these studies, the effect of PIN on PSA was analyzed either using prostate needle biopsy specimens, where the true incidence of PIN is often underestimated, or from prostatectomy specimens, where the effect of PIN and adenocarcinoma on serum PSA may be difficult to distinguish. By reviewing needle biopsy specimens, Brawer & Lange suggested that the presence of PIN might result in an elevation of serum PSA (7). However, this study could not exclude the presence of associated prostate cancer, which could have accounted for the elevation of PSA. Ronnett et al. reviewed 65 radical prostatectomy specimens with small volume of cancer and found that the volume of PIN did not correlate with preoperative serum PSA levels (9). Similarly, by studying 195 radical prostatectomy specimens removed for prostate cancer, Alexander et al. found no correlation between the presence of PIN in the specimen and preoperative serum PSA (8).

Table 2 - Incidence of high-grade prostatic intraepithelial neoplasia (HGPIN) in cystoprostatectomy specimens.

Cystoprostatectomy	HGPIN with Ca (%)	HGPIN no Ca (%)	Total PIN
Abbas et al., 1996 (15)	15/40 (38)	4/40 (10)	19
Yang et al., 1999 (16)	12/16 (75)	11/31 (36)	23
Kim et al.*	21/21 (100)	25/40 (63)	46
Troncoso et al., 1989 (17)	27/27 (100)	28/39 (72)	55
Total	75	68	143

*Current study

CONCLUSIONS

The prevalence of isolated high-grade PIN was 63% in patients undergoing cystoprostatectomy for bladder cancer. Extensive high-grade PIN (65%) was more likely to be associated with prostatic adenocarcinoma than focal high-grade PIN (31%). Isolated high-grade PIN is not an uncommon finding. However, as high-grade PIN does not appear to result in a significant elevation of serum PSA, prostatic adenocarcinoma must be ruled out as the source for an elevated PSA in a patient with a high serum PSA and an isolated high-grade PIN on needle biopsy.

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EDITORIAL COMMENT

The problem addressed in this article is significant, and the effort involved in completing this project is appreciated. High-grade prostatic intraepithelial neoplasia (HGPIN) is considered to be the most likely precursor of peripheral zone adenocarcinoma, and its presence on needle biopsy is associated with an approximately 30% likelihood of finding adenocarcinoma on subsequent biopsies. In the current study, the authors stated that adenocarcinoma must be ruled out in patients with a high serum PSA and an isolated high-grade PIN on needle biopsy, as HGPIN by itself does not seem to elevate the levels of serum PSA because it does not disrupt the basal membrane.

Numerous studies have assessed the relationship of HGPIN to prostate cancer, but usually they have been carried out in needle core biopsies, that are prone to sampling variation. This review was made in cistoprostatectomy specimens from patients with bladder carcinoma, avoiding the sampling error that can exist in needles biopsies or transurethral resections.

Routine use of serum PSA has increased the detection rate of prostatic adenocarcinoma. Therefore, the diagnosis of isolated HGPIN without carcinoma in a patient with increased levels of serum PSA should force the urologist to carry out a systematic biopsy of the prostate to rule out adenocarcinoma.

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