Over-diagnosis of high-grade prostatic intraepithelial neoplasia: a prospective study of 251 cases

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Accepted for publication 11 May 2007

OBJECTIVE
To assess the magnitude and causes of over-diagnosis of prostatic intraepithelial neoplasia (PIN), as large differences are reported in the incidence of high-grade PIN, probably because of the variance in diagnosis and interpretation.

PATIENTS AND METHODS
Two urological pathologists prospectively reviewed 251 consecutive patients, received in consultation and who were diagnosed and finalized by outside pathologists as having PIN.

RESULTS
The diagnosis of PIN was confirmed in 191 patients (incidence of concordance 76.1%, true positive) and refuted in 60 (discordance 23.9%, false positive). The most common histopathological findings misinterpreted as PIN included basal cell hyperplasia, benign epithelium, low-grade PIN, reactive changes, cribriform hyperplasia, atrophy, and post-atrophic hyperplasia.

CONCLUSIONS
There is a high rate of over-diagnosis of PIN, usually by misinterpretation of benign mimics. This significant error rate might account for some of the reported differences in the incidence of PIN and the variable predictive accuracy for cancer.

KEYWORDS
prostate cancer, prostatic intraepithelial neoplasia, over-diagnosis, basal cell hyperplasia

INTRODUCTION
High-grade prostatic intraepithelial neoplasia (PIN) was first described more than two decades ago, and since then its significance as the pre-invasive stage of prostatic adenocarcinoma has been confirmed repeatedly at many international consensus conferences and by >2000 published reports in animal models and humans (PubMed search, D. Bostwick, August, 2006, unpublished findings). Despite this great interest, interobserver variability persists, resulting in different reported incidences and disparate recommendations for the clinical response to the isolated finding of PIN on biopsy. Variance in the incidence of PIN in contemporary publications probably results from differences in the number of biopsies obtained (sampling variation), patient biopsy selection factors, and perhaps most importantly, variance in diagnosis and interpretation of PIN.

We undertook the present prospective study to determine the magnitude of over-diagnosis and to identify the histopathological mimics that are most likely to cause misinterpretation. Interobserver variation was previously measured retrospectively, but the present study is, to our knowledge, the first to prospectively measure the rate of false-positive diagnoses of PIN and to document the causes of over-diagnosis.

PATIENTS AND METHODS
We prospectively evaluated all 'second-opinion' prostate biopsies referred to one of us (D.G.B.) between 23 March and 25 April 2006. The study group consisted of second-opinion cases diagnosed and finalized by the extramural referring pathologist as high-grade PIN ('high-grade PIN', 'PIN2', 'PIN3' and 'PIN2-3'); this study criterion ensured a valid diagnostic comparison of the outside opinions with the study pathologists' opinions. We excluded cases with coexistent atypical small acinar proliferation (ASAP) suspicious for but not diagnostic of malignancy, or cancer, in any of the biopsies, as these diagnoses alone or combined with PIN might have a significant clinical effect on patient care, as such findings necessitate repeat biopsy or treatment, and probably diminish or eclipse the clinical significance of high-grade PIN. These study criteria ensured an exclusive focus on PIN as an isolated finding. Also excluded were cases in which the purported focus of PIN was not dotted on the slide, precluding an accurate assessment of what microscopic finding was interpreted as diagnostic. Patients with a previous history of prostate cancer with or without treatment were also excluded.

Each case was prospectively reviewed by both authors, and diagnostic agreement was reached in each case. The presence of the following was recorded: patient age, previous clinical and pathological findings, serum PSA level, DRE findings, method of specimen collection (biopsy or transurethral resection), site within the prostate, number of foci of each mimic of PIN, number of acini involved, volume of each mimic of PIN (as measured by ocular micrometer on a microscope), the presence of inflammation within 100 μm of the focus (measured by ocular micrometer), and the findings of immunohistochemical stains when available. When there was heterogeneity, only the most severe finding in each case was recorded.

RESULTS
During the study period 251 cases were received in consultation with the finalized diagnosis of isolated high-grade PIN. Four other cases were excluded because there were no slide markings designating the site of the
The diagnosis of high-grade PIN was confirmed in 191 cases (incidence of concordance of 76.1%, true positive) with an incidence of discordance of 23.9% (false-positive); the final diagnoses in discordant cases are shown in Table 1. Basal cell hyperplasia and atypical basal cell hyperplasia (basal cell hyperplasia with prominent nucleoli) (Fig. 1) collectively accounted for most over-diagnoses (32% of the total; 20% and 12%, respectively). Benign epithelium of the non-central zone (Fig. 2), central zone (Fig. 3), urothelium-lined prostatic ducts and ductules, and seminal vesicles accounted for 30% of over-diagnoses (17%, 8%, 3% and 2%, respectively). One case of benign non-central zone epithelium consisted of a solid nest of non-atypical basal cells with tangential cutting. Low-grade PIN (Fig. 4) and reactive changes each accounted for 17% of over-diagnoses, including two reactive cases with prominent coexistent inflammation. Rare over-diagnoses of PIN included clear cell cribriform hyperplasia, atrophy, and post-atrophic hyperplasia. The histopathological images of the 60 discordant are available for review at www.bostwicklaboratories.com.

The mean (range) age of the patients over-diagnosed with PIN was 62.4 (44–80) years. Nine patients had a history of high-grade PIN (previous slides not available for our review for confirmation), eight had no previous history of PIN, and no history was available in 43. The mean serum PSA level was 4.0 (0.7–9.4) ng/mL in 17 cases; PSA was reportedly ‘elevated’ in 15 others and no value was provided in the remaining 28. The DRE was abnormal in four patients, normal in one and not reported in the remaining 55. Referring pathologists’ diagnoses included ‘high-grade PIN’ in 42, ‘PIN 2’ in eight, ‘PIN 2–3’ in two, ‘PIN 3’ in four and ‘PIN not otherwise specified’ in four.

Specimens consisted of 56 needle biopsies and four transurethral resections. PIN was over-diagnosed on the left in 24 cases, the right in 21 and the location was not reported in 15 others; all cases were unilateral, but there were multiple separate foci over-diagnosed as PIN in seven cases. The mean (median, range) number of involved acini was 4.7 (3, 1–35); the mean volume of over-diagnosed PIN was 4 (0.08, 0.031–90) µL.
There was adjacent inflammation in six cases (10%), consisting of mild or moderate chronic inflammation; in one case there were additional cholesterol clefts with focal granulomatous inflammation. Immunohistochemical stains were available in 11 cases, including high-molecular weight cytokeratin (three) and combined triple stain of high-molecular weight cytokeratin, p63 and racemase (eight).

**DISCUSSION**

There was a significant incidence of over-diagnosis of high-grade PIN (24%) in this prospective study of many contemporary prostate biopsies. A wide variety of benign conditions were misinterpreted as PIN, including basal cell hyperplasia, benign epithelium, low-grade PIN, reactive changes, cribriform hyperplasia, atrophy, and post-atrophic hyperplasia. There were no cases of adenocarcinoma reported as high-grade PIN.

The mean (range) reported incidence of isolated high-grade PIN is 9 (4–16)% of prostate biopsies, resulting in ≈115 000 new cases annually [1]. The incidence and extent of PIN increase with patient age [2,3] and vary according to the population of men under study [4]. The lowest likelihood is in men participating in PSA screening and early detection studies, with an incidence of PIN in biopsies of 0.7–20% [4]. Men assessed by urologists in practice have PIN in 4.4–25% of contemporary needle biopsies. Interobserver agreement for high-grade PIN is ‘good to excellent’ according to κ statistics of retrospective studies, but the incidence of over-diagnosis in a prospective study has not previously been reported [5].

PIN has a high predictive value for cancer, although recent reports based on obtaining more cores have shown a lower predictive value [6–9]. The main factor accounting for the decline in predictive value is the use of extended biopsy techniques that result in more thorough prostate sampling and in higher cancer detection rates. In a recent report, the investigators showed that with six-core biopsies for both the initial and re-biopsy, the risk of cancer was 14.1%, compared to 31.9% in the group that had eight-core or more biopsies on follow-up with an initial six-core biopsy. Those authors found that the risk of cancer on biopsy within 1 year after a diagnosis of PIN (13.3%) was relatively low if good sampling (eight or more cores) was used initially [9].

Another plausible explanation for those results might be that backward probability is usually based on retrospective evidence, whereas forward probability is usually based on prospective evidence; consequently, backward probability is often easier to determine. Many researchers do not distinguish between these two probabilities, falsely concluding that the probability of a risk factor in patients with the disease is the probability of the disease occurring in people with the risk factor. The use of backward probability as a substitute for forward probability is a common fallacy in medical practice and might result in false attribution of causation [10].

There are many limitations and biases in the present study. First, we used the reproducibility of the diagnosis of PIN (second review of pathological material) as a surrogate ‘reference’ standard, but this is not an independent standard and represents a measure of precision rather than accuracy [11]. Second, there is considerable variation in the quality of histological sections referred from outside pathology laboratories that might have adversely affected our ability to identify high-grade PIN, thereby creating an ascertainment bias. Third, the study design used an unblinded review of biopsies enriched for PIN with the original (outside) diagnosis known at the time of review, creating potential under-interpreting bias [11]; the degree of such bias in this setting has not been measured in surgical pathology practice. Fourth, we chose to study relatively many consecutive consultation cases over a 1-month period in an attempt to minimize selection bias, but such cases are not random and thus might not be representative of all patients with PIN. Fifth, no attempt was made to reach a diagnostic consensus with the referring pathologist, so our results cannot distinguish between disagreements in opinion and true errors [11]. Sixth, our results might underestimate the frequency of over-diagnosis of PIN because we excluded cases with combined PIN and ASAP or adenocarcinoma. Finally, in this study we only measured the frequency of a false-positive diagnosis of PIN and not false-negative diagnosis, so the total level of diagnostic inaccuracy for this microscopic finding is unknown.

The over-diagnosis of PIN in clinical practice results in concern by both patient and clinician about subsequent malignancy, and in unnecessary repeat biopsies. In clinical trials that rely on referring histopathological diagnoses as an entry criterion, this lack of diagnostic precision contaminates the study population and might lead to erroneous conclusions; a central pathology review is recommended in this setting [12].

Subspecialization in surgical pathology (as measured in dermatopathology practice) resulted in a small but significant reduction in the diagnostic error rate (up to 1.4%) [11].

In conclusion, ≈24% of reported cases of high-grade PIN were reinterpreted upon review as benign mimics. This high rate of over-diagnosis might account for the variation in the incidence of reported PIN in contemporary publications.

**CONFLICT OF INTEREST**

None declared.

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Abbreviations: PIN, prostatic intraepithelial hyperplasia; ASAP, atypical small acinar proliferation; H&E, haematoxylin and eosin.