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EXTENT OF HIGH-GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA IS NOT A PREDICTOR OF CANCER AT REPEAT BIOPSY

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Objective High-grade prostatic intraepithelial neoplasia (PIN) is a well accepted precursor of invasive prostate cancer. Most investigators agree that a diagnosis of high-grade PIN warrants repeat transrectal ultrasound guided biopsy. We set out to investigate risk factors for cancer among a modern cohort of men with isolated high-grade PIN.

Material and Methods The Princess Margaret Hospital has a comprehensive database of 6249 TRUS procedures over the past 8 years. We searched this dataset for the following parameters: a) diagnosis of high-grade PIN between 1997 and 2003; b) absence of atypia or cancer and c) repeat prostate biopsy to rule out cancer. Additional covariates assessed were: age, prostate specific antigen (PSA) level at the time of biopsy, digital rectal examination (DRE) findings, transrectal ultrasound (TRUS) stage, TRUS volume, and the amount of PIN at biopsy (defined as one core vs. greater than one core by review of pathology reports). All data were tabulated and univariate (chi-square/t-tests) as well as multivariate (logistic regression) analyses were performed. All significance testing was two-sided with $p<0.05$ considered as significant.

Results A total of 130 patients had a diagnosis of high-grade PIN and underwent repeat biopsy. Among this cohort, 41 patients (31.5%) had cancer at re-biopsy. The Gleason sum distribution for these tumors was: 6 in 32 patients, 7 in 8 patients and 9 in 1 patient. Among the entire cohort the mean age was 64.1 years (range 37-78); PSA was 8.3 ng/ml (range: 0.28-70.2); and prostate volume was 65.43 cc (range 16-182.9). Fifteen patients (11.5%) had abnormal DRE, 53 (40.8%) had hypo-echoic lesions at TRUS, and 46 (35.4%) had more than one core high-grade PIN. On uni-variate analysis, the presence of an abnormal TRUS (22 of 52 with hypo-echoic lesions vs. 19 of 76 without hypo-echoic lesions, $p=0.039$) and the prostate volume (mean volume 69.66 cc for benign re-biopsies versus 56.89 cc for positive repeat biopsies, $p<0.05$) were significantly different between men with and without cancer at repeat biopsy. On logistic regression analysis, however, only the volume remained a significant predictor of cancer ($p=0.028$). There was no association between Gleason score at biopsy (6 vs > 6) and the extent of PIN at first biopsy ($p=0.86$).

Conclusions: In a modern cohort of men with high-grade PIN, PSA, DRE and age are not predictive of cancer at re-biopsy. There was no association between Gleason score at biopsy (6 vs > 6) and the extent of PIN at first biopsy. The prostate volume was the only significant predictor of cancer at re-biopsy.

Keywords: prostatic intraepithelial neoplasia, prostate, prostate volume

INTRODUCTION

Prostatic intraepithelial neoplasia (PIN) is characterized by cellular proliferation of pre-exisiting ducts, ductules and glands, with cytological changes similar to cancer, including nuclear and nucleolar enlargement[1]. Generally, PIN has been classically divided into low and high grade[2]. High-grade PIN which is considered the most important precursor of prostate cancer[3] is characterized by basal cell layer disruption, an increased proliferative

Table 1: Characteristics of the Patient Cohort

Parameter	Mean/Range	No (%)
Age	64.1 (37 – 78.0)	
PSA (ng/ml)	8.3 (28 – 70.2)	
Volume (cc)	65.4 (16 – 182.9)	
DRE (abnormal)		15 (11.5%)
TRUS (abnormal)		53 (40.8%)
Cancer		41 (31.5%)
Gleason sum		
6		31 (40.4%)
7		8 (10.4%)
8		1 (1.3%)
Extent of PIN		
1 core		86 (64.6%)
> 1 core		46 (35.4%0

potential and nuclear and nucleolar abnormalities. Different architectural patterns have been described; however the clinical significance of these remains unclear. High-grade PIN is found in 0.7-23% of prostatic needle biopsies[4]. Prostate cancer is found in 22-100% of high-grade PIN on repeated biopsy[5]. Because the general consensus of opinion is that high-grade PIN is closely associated with prostate cancer, close follow-up of these patients with repeated biopsies is always recommended. However, it is unclear which clinical predictors are important to identify patients at true high risk for prostate cancer after a first biopsy with high-grade PIN. Therefore we designed a retrospective study looking at predictors of cancer at re-biopsy among men with high-grade PIN at the first biopsy.

MATERIAL AND METHODS

The Princess Margaret Hospital, Toronto, Canada, has a comprehensive database of 6249 TRUS procedures over the past 8 years. We searched this dataset for the following parameters: a) diagnosis of high-grade PIN between 1997 and 2004; b) absence of atypia or cancer and c) repeat prostate biopsy to rule out cancer. Additional covariates assessed were: age, prostate specific antigen (PSA) level at time of biopsy, digital rectal examination (DRE) findings, transrectal ultrasound (TRUS) stage, TRUS volume, and amount of PIN at biopsy (defined as one core being positive or more than one core by review of pathology reports). All needle biopsies were reviewed by two of our institute's genito-urinary pathologists. All data were tabulated, and univariate (chi-square/t-tests) and multivariate (logistic regression) analyses were performed. All significance testing was two-sided with $p<0.05$ considered significant.

RESULTS

A total of 130 patients had a diagnosis of high-grade PIN and underwent repeat biopsy. Among the entire cohort, the mean age was 64.1 years (range 37-78); PSA was 8.3 ng/ml (0.28-70.2) and the prostate volume was 65.43 cc (range 16-182.9). In addition, 15 patients (11.5%) had abnormal DRE, 53 patients (40.8%) had hypo-echoic lesions at TRUS, and 46 (35.4%) had more than one positive core of high-grade PIN. Forty-one patients (31.5%) had cancer at re-biopsy. The Gleason sum distribution for these tumors was: 6 in 32 , 7 in 8 and 9 in 1 patient(s). (Table 1) The interval between biopsies ranged from 1 – 5 months (mean 2 months).

Univariate analysis revealed that the presence of an abnormal TRUS (in 22 of 52 patients with hypo-echoic lesions vs. 19 of 76 patients without hypo-echoic lesions, $p=0.039$) and the prostate volume (mean volume 69.66 cc for benign re-biopsies vs. 56.89 cc for positive repeat biopsies i.e cancer, $p<0.05$) differed significantly between men with and without cancer at repeat biopsy (Table 2), while on multivariate analysis using logistic regression, only the volume remained a significant predictor of cancer ($p=0.028$). There was no association between Gleason score at biopsy (6 vs. > 6) and the extent of PIN at first biopsy ($p=0.86$). Other covariates such as age, PSA, abnormal DRE, hypo-echoic lesions on TRUS were not predictors of the diagnosis of prostate cancer on repeat biopsy.

DISCUSSION

The reported incidence of high-grade PIN on biopsy ranges from 1.5% to 16.5%[6], with an average of 6%. The most likely explanation for this variation is interobserver threshold. The distinction between low- and high-grade PIN is

Table 2: Statistical Analysis of all Covariates

Covariate	Cancer	No Cancer	P-Value	Adjusted P-Value
DRE (abnormal)	6/14 (42.9%)	35/115 (30.4%)	0.37	0.78
TRUS (abnormal)	22/52 (40.7%)	19/ 76 (25.0%)	0.04	0.12
Extent of PIN	17/46 (36.9%)	24/ 84 (28.6%)	0.40	0.30
Volume (cc)	56.89 ± 27.5	69.67 ± 35.57	0.04	0.03
Age (years)	64.92 ± 6.94	63.65 ± 7.81	0.38	0.18
PSA (ng/ml)	8.45 ± 4.25	8.06 ± 7.91	0.76	0.76

based on the prominence of the nucleoli. This is a subjective exercise, and those pathologists with a lower threshold as to what defines prominent nucleoli will have a higher incidence of high-grade PIN. Other plausible explanations for the variation in the reported incidence of high-grade PIN relate to the fixative used and to differences in sampling. The largest studies reported a 23% to 35% risk of cancer on subsequent biopsy[7], others have found a 30-50% chance of diagnosing cancer over 3-5 years[9]. PIN by itself does not give rise to elevated serum PSA values. Repeat biopsy has been performed when high-grade PIN is found on needle biopsy, although there may be some men with a relatively low risk of subsequently diagnosed cancer. For patients with high-grade PIN on needle biopsy, there are conflicting studies as to whether serum PSA levels, the results of DRE examination and TRUS findings can enhance the prediction of who is more likely to have cancer on repeat biopsy. Park et al. conducted a study similar to ours and did not find any variables that could predict the diagnosis of cancer in subsequent biopsies[10]. Epstein et al. studied a number of clinical variables and none could predict the risk of cancer on repeat biopsy. The only independent histologic predictor of cancer at diagnosis was the number of cores with high-grade prostatic intraepithelial neoplasia; the risk of cancer was 30.2% with 1 or 2 cores, 40% with 3 cores and 75% with more than 3 cores[7]. It was not clear if these results maintained statistical significance on multivariate analysis.

In our study, 41 patients (31.5%) were found to have cancer on repeat biopsy which is similar to other reports. The interbiopsy interval ranged from 1 – 5 months (mean 2 months). Most of our patients were re-biopsied within 1 – 2 months, and therefore we did not examine, whether the interbiopsy interval had an effect on the cancer detection rate.

A critical factor which has been demonstrated to predict the risk of cancer on repeat biopsy is the extent of the initial and subsequent sampling on needle biopsy. It has been demonstrated in several studies that if there is more extensive sampling on needle biopsy (i.e. greater than eight cores) from both the initial and subsequent biopsies, the risk of associated cancer following a diagnosis of high-grade PIN decreases significantly. None of our patients had sextant biopsies, 10 cores were always obtained on the first biopsy. The presence of high-grade PIN on the pathology report warranted extensive sampling, i.e 12 cores.

The presence of an abnormal TRUS (in 22 of 52 patients with hypo-echoic lesions vs. 19 of 76 patients without hypo-echoic lesions, $p=0.039$) and the prostate volume (mean volume 69.66 cc for benign re-biopsies vs. 56.89 cc for positive repeat biopsies, $p<0.05$) differed significantly between men with and without cancer at repeat biopsy. This was also reported by De Wolf et al. who found that the volume could predict a subsequent diagnosis of cancer on re-biopsy, $p=0.04$[11]. However, it is not clear whether this statistical significance would be of clinical value based on our current knowledge. Unlike in the report by Epstein, the number of cores involved with PIN was subgrouped into 1 versus more than 1 core and there was no association between Gleason score at biopsy (6 vs. > 6) and the extent of PIN at first biopsy ($p=0.86$).

On logistic regression analysis, the volume remained the only significant predictor of cancer ($p=0.028$). Other co-variates such as

age, PSA and DRE could not predict the diagnosis of cancer on re-biopsy.

Our current study, as well as reports by others, supports the hypothesis that patients with high-grade PIN at initial biopsy are at high risk of developing cancer and that such patients should, therefore, be followed clinically every 6-12 months with a repeat biopsy as well. There appears to be no factor that could predict the results of the repeat biopsy except for the prostate volume. We continue to offer patients with high-grade PIN on biopsy a re-biopsy to be able to detect cancer at an early stage, although it is still a matter of controversy which patients would truly benefit from such repeat biopsies.

We conclude that in a modern cohort of men with high-grade PIN, PSA, DRE and age were not found to be predictive of cancer at re-biopsy. There was no association between Gleason score at biopsy (6 vs. > 6) and the extent of PIN at first biopsy. The prostate volume was the only significant predictor of cancer at re-biopsy.

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RESUME

La néoplasie intra-épithéliale prostatique de haut grade n'est pas un facteur prédictif de cancer à la biopsie répétée

Objectifs: La néoplasie intra-épithéliale prostatique de haut grade (PIN) est un précurseur bien connu de cancer de la prostate invasif. La plupart des investigateurs consentent qu'un diagnostic de PIN de haut grade justifie la répétition des biopsies transrectales écho-guidées. Nous avons eu l'intention d'enquêter sur les facteurs de risque pour cancer parmi une cohorte moderne d'hommes avec haut grade de PIN. **Patients et méthodes:** L'Hôpital de la Princesse Margaret a une base de données complète de 6249 procédures de TRUS sur les 8 années passées. Nous avons cherché ce dataset avec les critères d'inclusion suivants : a) diagnostic de PIN de haut grade entre 1997 et 2003; b) absence d'atypies ou cancer et c) biopsie répétée de la prostate éliminant le cancer. Les covariantes supplémentaires étaient: l'âge, l'antigène spécifique de la prostate (PSA) au moment des biopsies, les conclusions du toucher rectal (DRE), la TRUS, le volume à la TRUS, et le taux de PIN aux biopsies (défini comme focal ou plus que focal lors de la révision des rapports de la pathologie). Toutes les données ont été disposées en tableau et des analyses univariées (tests chi square/t) et multivariées ont été réalisées. **Résultats:** Un total de 130 patients avait un diagnostic de PIN de haut grade et

ayant subi une deuxième série de biopsies. Parmi cette cohorte, 41 patients (31.5%) avaient le cancer à la re-biopsie. Les scores de Gleason pour ces tumeurs étaient: 6 chez 32 patients; 7 chez 8 patients et 9 chez 1 patient. Parmi la cohorte entière l'âge moyen était 64.1 années (37-78 ans); la PSA était de 8.3 (0.28-70.2); et le volume de la prostate était de 65.43 grammes (16-182.9). Quinze patients (11.5%) avaient un DRE anormal, 53 patients (40.8%) avaient des lésions l'hypo-echogènes à la TRUS, et 46 (35.4%) avaient un PIN de haut grade plus que focal. Sur l'analyse univariée, la présence d'un TRUS anormal (22 de 52 avec lésions hypo-echogènes contre 19 de 76 sans lésions, p = 0.039) et le volume de la prostate (volume 69.66 moyen pour re-biopsies bénignes contre 56.89 pour les biopsies répétées positives, p <0.05) était considérablement différent entre patients avec et sans cancer à la re-biopsie. Cependant, sur l'analyse multivariée, seulement le volume est resté un facteur prédictif significatif de cancer (p=0.028). Il n'y avait aucune association entre le score de Gleason à la re-biopsie (6 contre> 6) et l'importance du PIN à la première biopsie (p=0.86). **Conclusions:** Dans une cohorte moderne de patients avec PIN de haut grade, PSA, DRE et âge ne sont pas prédictifs de cancer à la re-biopsie. Il n'y avait aucune association entre le score de Gleason, la re-biopsie (6 contre> 6) et l'importance du PIN à la première biopsie. Le volume de la prostate était le seul facteur prédictif de cancer à la re-biopsie.

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