Prostatic intraepithelial neoplasia in TURP specimens and subsequent prostate cancer

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Purpose: *Prostatic intraepithelial neoplasia (PIN) is considered as a precursor lesion for adenocarcinoma of the prostate. Most data supporting this relationship comes from the short-term follow-up of patients with repeated biopsies. We report a study in which patients were followed-up for 11 years to assess the relationships between the presence of high grade PIN, low grade PIN, and atypical adenomatous hyperplasia (AAH) and the subsequent occurrence of prostate cancer.*

Materials and methods: *For 601 men treated by TURP in 1990-1993, prostate specimens were reviewed to assess the presence of high grade PIN, low grade PIN, and AAH. Incidental carcinoma was observed in 67 men. Follow-up of the 534 men without incidental prostate cancer was conducted until December 2003 and 24 new prostate cancers were diagnosed. Multivariate regression models were used to assess the relationships between PIN and AAH and prostate cancer on both cross-sectional and prospective data.*

Results: *High grade PIN (odds ratio (OR) = 6.16, 95% confidence interval (CI): 3.28-11.58), low grade PIN (OR = 3.06, 95% CI: 1.45-6.46), and AAH (OR = 2.06, 95% CI: 1.00-4.29) were significantly associated with incidental prostate cancer. In the prospective study, only high grade PIN was associated with a statistically significant increased risk of prostate cancer: hazard ratio = 3.12, 95% CI: 1.15-8.49.*

Conclusion: *Although high grade PIN, low grade PIN, and AAH were all associated with incidental prostate cancer, the long-term prospective study showed that only high grade PIN was a significant determinant of the subsequent occurrence of prostate cancer.*

Key Words: prostatic neoplasms, prostatic intraepithelial neoplasia, atypical adenomatous hyperplasia, detection, follow-up

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Introduction

Two decades ago, two distinct histopathologic entities were identified as potential precursors of prostatic adenocarcinoma: prostatic intraepithelial neoplasia (PIN)[1] and atypical adenomatous hyperplasia (AAH).[2,3] PIN is defined as the abnormal proliferation within the lining of prostatic ducts, ductules, and acini of foci of cellular dysplasia and carcinoma in situ without stromal invasion. PIN was originally graded 1 to 3 but current recommendations recognize two grades of PIN: low grade PIN (corresponding to former grade 1) and high grade PIN (former grades 2

and 3).[4] High grade PIN is now accepted as the most likely preinvasive stage of adenocarcinoma of the prostate.[4-6] AAH is characterized by a circumscribed proliferation of closely packed small glands that tend to merge with the surrounding histologically benign glands. AAH resembles well differentiated adenocarcinoma but preservation of the basal cell layer excludes this diagnosis.[2,6,7] The evidence supporting the hypothesis of a transition from AAH to carcinoma is presently weak.[5,7] PIN and adenocarcinoma are more often observed in the peripheral zone of the prostate while AAH is more frequent in the transition zone where benign prostatic hyperplasia (BPH) occurs.[7] Most prospective studies showing an association between high grade PIN and subsequent diagnosis of prostate cancer have been conducted on patients with PIN discovered on biopsies and followed-up for a short period of time.[4-6] This suggests that prostate cancer was most likely already present at the time of PIN diagnosis. In order to obtain stronger evidence of the temporal relationship between potential premalignant lesions and prostate cancer, prospective studies with longer follow-up should be conducted. A few such investigations have been reported based on patients treated by transurethral resection of the prostate (TURP) for BPH.[8-10] We report a cohort study in which a large number of men treated by TURP for BPH were followed-up for more than 10 years to assess the relationships between the presence of high grade PIN, low grade PIN, and AAH and the subsequent occurrence of prostate cancer.

Methods

As part of a case-control study of diet and prostate cancer conducted in the Quebec City area,[11] 610 men treated by TURP to relieve the obstructive symptoms of BPH were enrolled between October 1990 and May 1993. The research protocol was approved by the Research Ethics Committee of Laval University and of each participating hospital. All participants were hospitalized for a few days before TURP surgery. In the days preceding the intervention, PSA was determined for most patients. Patients with a prostate nodule were not included in the study population. A few patients with elevated PSA were also subjected to prostate biopsies in the peripheral zone. When this investigation was positive for prostate cancer, the patient was not included in the study population. During the hospital stay, the patients were interviewed on their life habits, diet, physical activities, and medical history. For all but nine patients, the prostate tissue removed at TURP was systematically reviewed by a single pathologist (B.T.) without knowledge of any patient information. For each patient, the pathologist examined every TURP chip for cancer, PIN, and AAH. On a pre-established coding form, he noted the presence or absence of AAH, low grade PIN, high grade PIN, and incidental carcinoma. The degree of extension of AAH and PIN was also noted. When prostate cancer was present, it was also recorded whether AAH and PIN was observed at proximity or at distance of the malignant lesion. Furthermore, the presence of BPH and its predominant type (epithelial, stromal, mixed) were also noted. Incidental carcinoma of the prostate was diagnosed for 67 men (incidental cases). The pathologist's assessment was conducted as part of a research project and his conclusions were not communicated to the patients and their treating physicians.

For the cohort follow-up, permission was obtained from the Commission d'Accès à l'Information du Québec to receive follow-up information concerning the 534 men without incidental prostate cancer from three registries: date and cause of death from the provincial mortality file (held by the Institut de la Statistique du Québec) for the years 1990 to 2003; occurrence of prostate cancer with date of diagnosis either from the provincial cancer registry (Fichier des tumeurs du Québec) for the years 1990 to 2000 or from the provincial registry of hospital stays (fichier Med-Écho) for the years 2001 to 2003. The cohort follow-up relied exclusively on record linkage with the provincial databases. There was no information available on clinical investigations, hospitalizations, test results, diagnoses and tumor characteristics during the follow-up. During the follow-up 193 men died and 24 were diagnosed with prostate cancer (new cases).

Patients' characteristics at the time of TURP were compared between those with incidental prostate cancer and those without this diagnosis using Student's t tests for continuous variables and Chi square tests for categorical data (Fischer's exact tests when required). The same approach was used to compare features associated with grade of PIN among patients presenting both PIN and incidental carcinoma. Logistic regression was used to estimate odds ratios, and their 95 % confidence intervals, for incidental prostate cancer associated with PSA, PIN and AAH.[12] Age was always included in the models to control confounding. For the prospective study conducted among the 534 patients not diagnosed with incidental prostate cancer, follow-up time was counted from the date of TURP until the first of the following events: diagnosis of prostate cancer, death, or scheduled end of follow-up on December 31, 2003.

TABLE 1. **Baseline characteristics of the 601 study participants according to the presence or absence of incidental prostate cancer (incidental cases)**

	Incidental cases n = 67	Non cases n = 534	P-value
Age (year) - Mean (SD)	71.0 (7.1)	68.4 (7.1)	0.004
Body Mass Index (kg/m^2)* - Mean (SD)	25.5 (3.7)	25.3 (3.9)	0.75
Living with wife – n (%)	55 (82)	458 (86)	0.42
Primary school – n (%)	44 (66)	287 (54)	0.18
Secondary school – n (%)	12 (18)	134 (25)	
Beyond secondary school – n (%)	11 (16)	113 (21)	
Never smoker - n (%)	6 (9)	85 (16)	0.32
Past smoker - n (%)	47 (70)	34 (64)	
Present smoker - n (%)	14 (21)	108 (20)	
Leisure time physical activities - n (%)	50 (75)	382 (72)	0.60
BPH epithelial** - n (%)	46 (75)	375 (70)	0.65
BPH stromal - n (%)	2 (3)	29 (5)	
BPH mixed - n (%)	13 (21)	128 (24)	

* Missing values for BMI for three cases and seven non cases
** Missing values for type of BPH for six cases and two non cases

Cox proportional hazards models were used to estimate hazard ratios of prostate cancer associated with PSA, PIN and AAH at baseline.[13] Age was always included in the models to control confounding. Hazard ratios are presented together with their 95% confidence intervals.

Results

In the cross-sectional study, men with incidental prostate cancer were older than those without, Table 1. Marital status, education, smoking, body mass index and physical activities were comparable in the two groups. There was no difference in the distribution of the types of BPH. Although PSA was elevated in both groups due to the presence of BPH, there were significantly more men with PSA ≥ 10 ng/mL in the group with incidental carcinoma: odds ratio (OR) = 2.81, 95% confidence interval (CI): 1.32-6.01, Table 2. Both low grade PIN and high grade PIN were significantly associated with increased odds ratios for prostate cancer: OR = 3.06

TABLE 2. **Age-adjusted odds ratios for incidental prostate cancer and 95% confidence interval (CI) associated with serum PSA, PIN and AAH among 601 men treated by TURP for BPH. Cross-sectional study, Quebec 1990-1992.**

	Categories	Incidental cases n = 67 n (%)	Non cases n = 534 n (%)	Odds ratio (95% CI)
PSA*	< 4.0 ng/mL	16 (31)	171 (48)	1.00
	4.0-9.9 ng/mL	19 (37)	124 (35)	1.55 (0.77-3.15)
	≥ 10 ng/mL	16 (31)	58 (16)	2.81 (1.32-6.01)
PIN	No PIN	34 (51)	445 (83)	1.00
	Low grade PIN	11 (16)	47 (9)	3.06 (1.45-6.46)
	High grade PIN	22 (33)	42 (8)	6.16 (3.28-11.58)
AAH	No AAH	56 (84)	491 (92)	1.00
	AAH	11 (16)	43 (8)	2.06 (1.00-4.29)

*missing values for PSA for 16 cases and 181 non cases

TABLE 3. **Age-adjusted hazard ratios for prostate cancer and 95% confidence interval (CI) associated with serum PSA, PIN and AAH among 534 men treated by TURP for BPH and without incidental prostate cancer in 1990-1992. Prospective study, Quebec, 1990-2003.**

	Categories	Cases n = 24 n (%)	Non cases n = 510 n (%)	Hazard ratio (95% CI)
PSA*	< 4.0 ng/mL	5 (25)	166 (50)	1.00
	4.0-9.9 ng/mL	6 (30)	118 (35)	1.52 (0.46-5.01)
	≥ 10 ng/mL	9 (45)	49 (15)	4.97 (1.66-14.90)
PIN	No PIN	18 (75)	427 (84)	1.00
	Low grade PIN	1 (4)	46 (9)	0.55 (0.07-4.09)
	High grade PIN	5 (21)	37 (7)	3.12 (1.15-8.49)
AAH	No AAH	22 (92)	469 (92)	1.00
	AAH	2 (8)	41 (8)	1.08 (0.26-4.62)

*missing values for PSA for two cases and 177 non cases

(95% CI: 1.45-6.46) and OR = 6.16 (95% CI: 3.28-11.58) respectively for low grade and high grade PIN. AAH was also associated with a statistically increased odds ratio for incidental carcinoma: OR = 2.06 (95% CI: 1.00-4.29). Further adjustment for the presence of PIN did not materially alter the association between AAH and incidental prostate. Patients with low grade PIN significantly differed (p = 0.0001) from those with high grade PIN by the number of glands involved. PIN was noted in more than 10% of glands examined respectively in 12% (7/58) of subjects with low grade PIN and in 44% (28/64) of those with high grade PIN. When both PIN and prostate cancer were present on the TURP specimens, high Gleason grade (greater or equal to 7) was more often associated (p = 0.01) with high grade PIN (9/22) than with low grade PIN (0/11).

In the prospective study, the median duration of follow-up was 11.2 years. Twenty-four new cases of prostate cancer were identified among the 534 men. The median duration between TURP and the diagnosis of prostate cancer was 7.3 years. Only five cases were diagnosed during the first 5 years of follow-up. Half of the new cases of prostate cancer were diagnosed from 7 to 11 years after TURP. Baseline PSA was associated with the occurrence of prostate cancer. In men with baseline PSA ≥ 10 ng/mL, the hazard ratio (HR) was 4.97 (95% CI: 1.66-14.90). High grade PIN was associated with a statistically significant increased risk of prostate cancer: HR = 3.12, 95% CI: 1.15-8.49, Table 3. On the other hand, neither low grade PIN (HR = 0.55, 95% CI: 0.07-4.09) nor AAH (HR = 1.08, 95% CI: 0.26-4.62) were associated with prostate cancer risk.

Discussion

Although AAH, low grade PIN and high grade PIN were associated in the cross-sectional study with the presence of incidental prostate cancer on TURP specimens, our long-term prospective study showed that only high grade PIN was a significant determinant of the subsequent occurrence of prostate cancer. These results are in agreement with the current state of knowledge concerning potential premalignant lesions which could be identified on prostatic tissue.[4-6]

Our results in the cross-sectional study should be compared to those of other studies that have examined the relationships between potential premalignant lesions and prostate cancer among patients treated by TURP. The prevalence of high grade PIN at the time of TURP among men without incidental carcinoma was higher in our study (7.9%) than in those published by Gaudin et al (3.2%),[8] Pacelli and Bostwick (2.8%)[9] and Mai et al (1.0%).[14] On the other hand, Skjørten et al reported a very high prevalence of high grade PIN in men without incidental carcinoma (50%).[15] The prevalence of AAH in TURP specimens without cancer was 8.1% in our study compared to 13%[14,15] and 6%[16] in previous studies. As in our study, both high grade PIN and AAH were significantly associated with incidental carcinoma in the study of Mai et al.[14] The OR for incidental carcinoma associated with high grade PIN was 3.9 in the study of Pacelli and Bostwick.[9] However, there was no significant association between high grade PIN and incidental carcinoma in the study of Skjørten et al.[15] This and the very high prevalence of high grade PIN reported for this study population suggests substantial misclassification in the assessment of PIN.

Our cohort study investigating the temporal relationship between PIN and the subsequent occurrence of new prostate cancers presents two weaknesses. First, prostate cancer may have been already present at the time of TURP but remained undiagnosed since systematic biopsies of the peripheral zone were not performed. Second, we relied exclusively on passive follow-up through record linkages. This approach ensured uniformity and consistency in the assessment of new cases, but the study suffers from the lack of any information on clinical follow-up, repeat PSA, biopsies or TURP. Furthermore, there was no data available on the tumor characteristics (stage, Gleason grade, PSA) for the new cases of cancer. It is likely that some prostate cancer cases diagnosed during the follow-up period were not reported to the provincial databases since both rely on hospitalizations and not on pathology reports. However, since PIN status was unknown to patients and treating physicians, under diagnosis should have been comparable in men with and without PIN. As a result of these errors, the observed hazard ratio of prostate cancer associated with high-grade PIN underestimates the real association.

Three studies have examined prospectively the clinical significance of high grade PIN among men treated by TURP but without incidental carcinoma.[8-10] Gaudin et al obtained follow-up information for 41 patients who had high grade PIN but no cancer on TURP material.[8] After a median follow-up period of 4.3 years, prostate cancer was diagnosed in nine patients. There was no control group for comparison. In a small prospective study, Pacelli and Bostwick followed up 16 patients with high-grade PIN on TURP material and 32 other patients without PIN matched for age and PSA level.[9] Prostate cancer was diagnosed in three men with PIN after a median follow-up period of 6 years while no case of prostate cancer was identified among the 32 men without PIN. The article provides no information on the duration of follow-up in this latter group of patients. A large population of 789 patients treated by TURP or transvesical enucleation and without incidental prostate cancer was followed for an average duration of 11 years in Norway.[10,15] Record linkage with the cancer registry was used to identify all new cases of prostate cancer. A total of 36 cases of prostate cancer were discovered. The prospective study showed no significant association between low grade PIN, high grade PIN, or AAH and prostate cancer. In fact, men with high grade PIN had a lower risk of subsequent prostate cancer than those without. Thus our study is the first to show a statistically significant positive association between high-grade PIN on TURP specimens and the risk of subsequent prostate cancer over the long term. Since the interval between the identification of PIN and the subsequent occurrence of prostate cancer in our prospective study was long, our results provide new information complementing that obtained from short follow-up of patients with PIN on biopsy. The clinical management of patients with BPH has changed since the time of initial data collection for this study. The pharmacological treatments have reduced and delayed the use of TURP to relieve the obstructive symptoms of BPH. Therefore, it is unlikely that our study could be reproduced in the future. Our findings could have nowadays-low clinical significance but they remain clearly relevant for the pathogenesis of prostate cancer.

Our results confirm that high grade PIN is an important predictive factor for prostate cancer for TURP specimens as well as for biopsy material.[4,18] The present study cannot demonstrate a direct progression from high grade PIN to prostate cancer. PIN and prostate carcinoma are multifocal diseases sharing strong genetic similarities.[4,17] Prostate cancer could have been present at the time of TURP, or have subsequently developed either from the evolution of a PIN lesion or not. In any case, the positive association between PIN and subsequent prostate cancer has prompted the Cancer Committee of the College of American Pathologists to recommend reporting the presence of PIN in TURP specimens.[19] Our data and those from previous studies,[4,9] suggest that PSA may further help in the identification of patients at higher risk of developing prostate cancer. □

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