

# Distribution of Inflammation, Pre-Malignant Lesions, Incidental Carcinoma in Histologically Confirmed Benign Prostatic Hyperplasia: A Retrospective Analysis

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## Abstract

**Objectives:** We analyze our experience on BPH through 20 years of histopathological examinations performed by the same pathologist.

**Methods:** We retrospectively reviewed all histopathological examinations performed from January 1979 to December 1998 in patients undergoing surgery in our urological clinic who were diagnosed with BPH. We limited our evaluation to the following variables in each BPH case analyzed: inflammatory aspects associated with BPH, presence of focal acinar atrophy, atypical adenomatous hyperplasia (AAH), prostatic intraepithelial neoplasia (PIN), incidental prostate carcinoma (IC). These histological variables were analyzed according to some clinical parameters such as age, prostate volume and serum PSA.

**Results:** The study population was comprised of 3942 cases with histological diagnosis of BPH. The mean patient age was  $68.85 \pm 7.67$  years. In particular, inflammatory aspects were associated with BPH in a high percentage of cases ( $43.1\% = 1700$  cases), predominantly as chronic inflammation. Observation of focal acinar atrophy significantly increased according to patient decade of age ( $p = 0.027$ ). There was a significant trend to increase with age decades ( $p = 0.036$ ) for high grade PIN. A significant difference was found in IC (T1a, T1b) distribution in the different decades of age and especially in regards to both T1a and T1b tumors, there was a trend to increase with patient age ( $p = 0.020$  and  $p = 0.025$ , respectively). On the contrary, the distribution of inflammatory aspects ( $p < 0.001$ ) and AAH ( $p = 0.003$ ) significantly varied according to prostate volume, and particularly in regards to chronic inflammation, there was a trend to increase depending on the prostate volume ( $p = 0.002$ ). Only the presence of T1b tumor but not of the other histological parameters associated to BPH, was able to significantly influence serum PSA.

**Conclusion:** In our analysis different histological variables associated to BPH are differently influenced by the age of patients and prostate volume, and they differently influence serum PSA levels.

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**Keywords:** Benign prostatic hyperplasia; Histopathology; Prostate volume; Prostatic intraepithelial neoplasia; Prostate neoplasms

## 1. Introduction

Clinical aspects of benign prostatic hyperplasia (BPH) are not necessarily related to the size of the

prostate but may be correlated with the histological composition of its volume [1]. Histopathological analysis may, therefore, also have clinical and practice relevance. Histological examination of the prostate must also include the description of some important aspects which may be present or associated with BPH and which may condition the progression of this disease.

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In this study, we focused our attention on the following variables analyzed during the histological examination for BPH: inflammatory aspects, lesions considered pre-neoplastic, and the incidental diagnosis of prostate cancer.

It is well recognized by both urologists and pathologists that BPH and inflammation can coexist [2,3], but the interrelationship between BPH and prostatic inflammation, and how one may influence the presentation of the other, is unknown [4].

On the other hand, putative pre-malignant lesions of the prostate gland have been recognized for a long time, and they may be associated with the histological diagnosis of BPH. Early investigations have revealed that prostate carcinoma is often associated with focal glandular atrophy [5]. Other authors have reported that focal prostatic glandular atrophy may occur in association with chronic inflammation [6,7]. Recent reports suggest that focal atrophy may be causally linked to prostate cancer and to other pre-neoplastic lesions [8]. However, autopsy studies of atrophy have rejected this concept, and data supporting reconsideration at this time are limited.

Atypical adenomatous hyperplasia (AAH) is another possible finding in the prostate that may be pre-malignant, but data on this lesion are much less convincing than data on prostatic intraepithelial neoplasia (PIN). Most cases of AAH are localized in the transition zone of the prostate [9,10]. On the contrary, occurrence of PIN in transurethral resection of prostate specimens is relatively uncommon [11].

The present study cannot be considered an epidemiological analysis for it reports only our experience on BPH through 20 years of histopathological examinations performed by the same pathologist (ADM). We reviewed a large number of pathological specimens obtained at resection of the prostate for BPH in our clinic. In this initial study, we primarily focused our analysis to aspects of BPH obtained from histopathological examinations, but we also tried to compare these data with some clinical parameters such as age of the patient, prostate volume, total prostate specific antigen (PSA) serum levels.

Therefore, the aim of this study was to:

1. analyze the distribution of inflammation, focal acinar atrophy, AAH, PIN, and IC in histologically confirmed BPH samples;
2. analyze their changes in different periods of examination (from 1979 to 1998);
3. analyze their relationships and their differences on the basis of classification of cases by patient age decade, prostate volume and surgical procedure;
4. analyze their effect on serum PSA levels.

## 2. Materials and methods

This is a retrospective, single center study. We reviewed all histopathological examinations consecutively performed from 1979 to 1998 in patients undergoing surgery in our urology clinic who were diagnosed with BPH. All histopathological examinations were performed by the same pathologist (ADM), and in each case all histological slides were reviewed by two pathologists without their having any knowledge of the clinical course of the patients. Inclusion into this study was based on the following criteria:

1. examination performed from January 1979 to December 1998;
2. examination obtained from surgical procedures for BPH [only transurethral resection of the prostate (TURP); open suprapubic prostatectomy (OP)] performed in our urology clinic;
3. tissue samples adequate for a complete histopathological evaluation;
4. histologically confirmed diagnosis of BPH;
5. no previous prostate surgery;
6. no clinical suspicion of prostate cancer.

We restricted our analysis to the period from 1979 to 1998 because this span corresponded to the working activity of our pathologist (ADM) in our clinic.

All histological examinations were obtained from patients who underwent surgery for voiding symptoms suggestive of BPH, all of whom presented a palpably benign prostate. Before 1989, the clinical suspicion of prostate cancer was mainly based on the digital rectal examination (DRE); from 1989 to 1998, serum prostate specific antigen (PSA) assay and transrectal ultrasonography (TRUS) were introduced as routine tests in all patients admitted to surgery for BPH. Every patient with an abnormal DRE, TRUS or a PSA  $\geq 4$  ng/ml underwent systematic TRUS-guided biopsies of the prostate. The routine assay of free (fPSA) and total PSA (tPSA) isoforms was introduced only after 1998.

Finally, a total of 3942 histopathological examinations with a confirmed BPH diagnosis fulfilled the criteria and was included in our analysis. Other 178 examinations were excluded from the review because these involved histological specimens considered inadequate. Specifically, 1621 examinations (41.1%) were obtained from TURP and 2321 (58.9%) from OP.

Prostate volume, preoperatively obtained by TRUS using the prolate ellipsoid formula [12], was available in only 2981 of our cases. Prostate size and weight were not measured *in vivo*.

Preoperative total serum PSA levels were available only in cases examined from 1989 to 1998. In these cases PSA determination was carried out prior to any prostatic manipulation, and prior to any biopsy or surgery of the prostate. In all cases the serum PSA concentration was determined with a Tandem-R PSA assay (Hybritech Inc., San Diego, CA).

In each of the 3942 cases, all prostate specimens obtained from surgery were previously fixed in 10% buffered formalin and embedded in paraffin by standard histological procedures. For TURP every chip and for OP all adenomas enucleated at surgery were processed and analyzed.

To validate the comparison over a 20-year period, in each case all histological slides were reviewed and re-classified using internationally accepted criteria. In each case, the histological diagnosis of BPH was confirmed and all histological sections were examined for evidence of the following variables: acute and chronic inflammation, focal acinar atrophy, postatrophic hyperplasia (PAH), atypical adenomatous hyperplasia, prostatic intraepithelial neoplasia, incidental carcinoma (IC).

In particular, in all cases, T classification of the IC was assigned according to TNM, and all data were adjusted retrospectively according to the 1997 classification system [13] (T1a: tumor involving  $\leq 5\%$  of the resected prostatic tissue; T1b: tumor involving  $>5\%$  of the resected prostatic tissue).

The term PIN was introduced in 1987 by Bostwick and Brawer [14]. Our pathologist initially referred to this lesion as intraductal dysplasia. All tissue samples were reviewed for the presence of PIN, and we re-classified the lesions using the modern concept of high grade PIN (HGPIN) and low grade PIN (LGPIN) [15].

All AAH lesions were confirmed using accepted criteria [16–18].

The presence of focal acinar atrophy was defined as one or more discrete foci of simple glandular atrophy (patches of atrophic epithelium within a background of surrounding normal-appearing non-atrophic epithelium) or as postatrophic hyperplasia (foci of crowded glands with small atrophic acini) [8,19].

All histological samples were also examined for the presence of inflammation associated with BPH. Acute inflammation was recorded when a neutrophilic infiltrate involved the glands as well the stroma often associated with glandular damage. The terms mild, moderate, and severe were used to indicate involvement of fewer than one-third, about two-thirds, or more than two-thirds of the tissue samples, respectively, by the acute inflammatory process. A mononuclear infiltrate around some of the ducts or acini was recorded as being a mild chronic inflammation. A more extensive, but localized, process involving about half of the ducts or acini with inflammatory infiltrate in the lumina and stroma was graded as being a moderate chronic inflammation. Severe chronic inflammation was diagnosed if in the tissue samples there was diffuse involvement of a mononuclear infiltrate of lymphocytes, plasma cells and histocytes [20].

Afterwards, the whole population of 3942 cases was divided into different groups on the basis of the period of examination, patient age, prostate volume and surgical procedure, so to analyze the influence of these clinical parameters on the distribution of the histological variables associated to BPH.

According to the period of observation we considered—group 1: 1979–1983; group 2: 1984–1988; group 3: 1989–1993; group 4: 1994–1998.

Based on their age, the patients were considered as being in one of four age decades—group 1: 50–59 years; group 2: 60–69 years; group 3: 70–79 years; group 4: 80–89 years. In this part of the study, in classifying cases in the four age decades, we included only examinations conducted on patients from 50 to 89 years of age. Between 1979 and 1998, 82 BPH cases of patients less than 50 years old and 115 of patients more than 89 years old were pathologically evaluated in our clinic.

According to prostate volume we considered—group 1: 30–39 cc; group 2: 40–49 cc; group 3: 50–59 cc; group 4: 60–69 cc; group 5: 70–79 cc; group 6: 80–89 cc. Only 41 cases presented a prostate volume  $>89$  cc. We obtained data on prostate volume for only 2981 cases (missing values: 961). For all other variables, we obtained data for each case (missing data: 0). Depending on the surgical procedure, we considered—group 1: open prostatectomy (OP); group 2: transurethral resection (TURP).

In the last part of this study we tried to analyze the effect of the histological variables on serum PSA levels. For the analysis of PSA we considered different groups of cases: (1) cases with only histological BPH (without the presence of the associated histological variables that we examined); (2) cases with BPH associated only with inflammation; (3) BPH associated only with focal atrophy; (4) BPH associated only with AAH; (5) BPH associated only with PIN; (6) BPH associated only with incidental carcinoma.

In this way we were able to analyze the effect of each single histological parameter on PSA levels. Finally 2130 of our cases in which serum PSA was available, responded to the criteria and were included in this sub-analysis.

### 2.1. Statistical analysis

Descriptive statistics were used to characterize the age of patients, prostate volume (mean  $\pm$  S.D., median and range) as well as the presence of inflammatory aspects, acinar atrophy, PAH, AAH, PIN, IC. Age of patient and prostate volume were used as continuous variables whereas other parameters were classified naturally and transformed into indicator variables. Statistical evaluations were performed either on the whole population of 3942 cases or on the different groups assigned on the basis of the period of examination, age decades, prostate volume and surgical procedure. Variations in the parameters per different group were reported. Chi-square ( $\chi^2$ ) tests to evaluate significant differences in the categorical distribution of the variables in the different groups, the Fisher's exact test, Kruskal–Wallis test, Mantel Trend tests and the Matel–Haenszel test to adjust comparison for other categorical variables were performed [21,22]. Linear regression models were also used. Spearman's correlation coefficients were calculated to measure the association among the different variables. Considering the high number of cases in this study, we assumed as significant only those correlation coefficients ( $r$ ) explaining more than 5% of the variance of one factor on the other ( $r \geq 0.2236$ ;  $r^2 = 0.05$  (5%)).

## 3. Results

Our analysis included 3942 histopathological examinations for BPH.

Table 1 summarizes data of the 3942 cases which satisfied the study criteria. In particular, inflammatory aspects were present in a high percentage (43.1% = 1700 cases) of cases, predominantly as chronic inflammation. Inflammation was mild in 78%, moderate in 21%, and severe in only 1% of these 1700 cases.

PIN was present in 2.1% of our cases with similar distribution for LGPIN (1.1%) and HGPIN (1.0%).

Incidental carcinoma was found in 5.5% of our cases, with a higher percentage for T1a (4.7%) as compared to T1b (0.8%) carcinomas. In T1a tumors, the distribution of Gleason score was  $<6$  in 89.7% and 6 in 10.3% of cases. None of T1a carcinomas showed a Gleason score of 7 or more. In T1b cases, the distribution of Gleason score was  $<6$  in 37.5%, 6 in 28.1% and 7 in 34.4% of cases.

In analyzing for a correlation between the different variables (inflammation, AAH, atrophy, PIN, incidental carcinoma), all associations were found to be very weak ( $r < 0.20$ ) and not statistically significant.

### 3.1. Results according to the period of observation

The distribution of the different variables in the four groups is described in Table 2; age of patients and

**Table 1**

Characteristics of the 3942 histopathological examinations included in the analysis

Variable	No. of cases	Percentage
Age (years)	66.85 ± 7.67 (median 67; range 45–94)	
Volume (cc)	58.87 ± 14.92 (median 60; range 30–200)	
Period		
1979–1983	524	13.3
1984–1988	629	16.0
1989–1993	1417	35.9
1994–1998	1372	34.8
Surgery		
TURP	1621	41.1
Open prostatectomy	2321	58.9
Inflammation		
Total	1700	43.1
Chronic	1180	29.9
Acute	520	13.2
Mild chronic	920	23.3
Moderate chronic	243	6.2
Severe chronic	17	0.4
Mild acute	402	10.2
Moderate acute	111	2.8
Severe acute	7	0.2
Atrophy	166	4.2
PAH	52	1.3
AAH	184	4.7
PIN	85	2.1
LGPIN	43	1.1
HGPN	42	1.0
Incidental carcinoma	217	5.5
T1a	185	4.7
T1b	32	0.8

prostate volume are reported as median values whereas other variables are described as percentages.

In particular the number of cases examined significantly increased from the first to the third period. Mean and median age of patients did not significantly vary from group 1 (66.92 ± 7.39; median 67 years) to group 4 (66.45 ± 7.44; median 67 years) ( $p = 0.216$ ) (Table 2).

On the contrary, mean and median prostate volume significantly decreased from group 1 (66.06 ± 12.99 cc; median 69 cc) to group 4 (57.48 ± 15.19 cc; median 58 cc) ( $p < 0.001$ ).

The distribution of cases in the two different categories of surgical procedure (OP, TURP) significantly and progressively varied from group to group ( $p < 0.001$ ), and there was a particular trend towards a decrease for OP and towards an increase for TURP from group 1 to group 4 (Table 2).

The distribution of PIN significantly varied in the four groups ( $p = 0.030$ ) (Table 2), and especially for HGPIN, there was a trend to increase from group 1 to group 4.

A significant difference ( $p < 0.05$ ) in the distribution of the other variables, IC, inflammation, atrophy, PAH and AAH in the different periods of examinations was found (Table 2), but a specific trend in data could not be found.

### 3.2. Results according to patient age

Distribution of the different variables in the four groups is described in Table 3; age of patients and prostate volume are reported as median values whereas other variables are described as percentages.

Most of our pathological examinations were obtained from patients in the sixth (1745 cases) and seventh (1274 cases) decade of age.

Mean and median prostate volume significantly increased from group 1 (57.15 ± 14.46; 57 cc) to group 4 (59.05 ± 15.31; 60 cc) ( $p = 0.003$ ).

Distribution of focal acinar atrophy significantly varied from group to group ( $p = 0.020$ ) (Table 3), and there was a trend to increase with decades of age (Fig. 1). Using group 1 (40–49 years) as the reference, patients in groups 2–4 were progressively more likely to have acinar atrophy: group 2 versus group 1: odds ratio 1.78 (95% confidence interval 1.23–2.62); group 3 versus group 1: odds ratio 2.13 (95% confidence interval 1.54–3.11); group 4 versus group 1: odds ratio 2.30 (95% confidence interval 1.63–3.54).

Regarding PIN, the distribution in the different decades of age significantly varied ( $p = 0.030$ ) (Table 3); for HGPIN, there was a significant trend to increase with age decades (Fig. 2). Using group 1 as the reference, patients in groups 2–4 were progressively more likely to present a HGPIN: group 2 versus group 1: odds ratio 1.42 (95% confidence interval 0.97–1.96); group 3 versus group 1: odds ratio 1.71 (95% confidence interval 1.24–2.65); group 4 versus group 1: odds ratio 3.28 (95% confidence interval 1.96–4.59).

A significant difference in the distribution of incidental carcinoma (T1a, T1b) in the different decades of age was found ( $p = 0.001$ ) (Table 3), and in particular, in regards to both T1a and T1b tumors, there was a trend to increase from group 1 to group 4 (Fig. 3). Using group 1 as the reference, patients in groups 2–4 were progressively more likely to have an incidental carcinoma: group 2 versus group 1: odds ratio 1.60 (95% confidence interval 1.13–2.35); group 3 versus group 1: odds ratio 2.53 (95% confidence interval 1.74–3.65); group 4 versus group 1: odds ratio 3.36 (95% confidence interval 1.80–4.34).

**Table 2**

Distribution of the different variables according to the period of observation

Variable	Group 1 (1979–1983)	Group 2 (1984–1988)	Group 3 (1989–1993)	Group 4 (1994–1998)
No. of cases ( $p < 0.001$ )	524	629	1417	1372
Age (years) ( $p = 0.216$ )	67	67	67	67
Volume (cm <sup>3</sup> ) ( $p < 0.001$ )	69	62	60	58
Surgery ( $p < 0.001$ ) (%)				
TURP	15.6	31.5	38.8	57.6
OP	84.4	68.5	61.2	42.3
Inflammation ( $p = 0.003$ ) (%)				
Total	43.1	36.7	45.3	43.8
Chronic	23.1	23.8	31.6	33.6
Acute	20.0	12.9	13.7	10.2
Atrophy ( $p < 0.001$ )	3.2	1.6	6.1	3.8
PAH ( $p = 0.020$ )	0.8	0.3	1.9	1.4
AAH ( $p < 0.001$ )	4.4	1.3	5.3	5.7
PIN ( $p = 0.030$ ) (%)				
Total	1.7	1.7	2.5	2.2
LGPIN	1.1	0.6	1.4	0.9
HGPIN	0.6	1.1	1.1	1.3
Incidental carcinoma ( $p = 0.002$ ) (%)				
Total	4.0	3.5	7.2	5.2
T1a	3.6	3.3	6.4	4.0
T1b	0.4	0.2	0.8	1.2

**Table 3**

Distribution of the different variables according to patient decades of age (years)

Variable	Group 1 (50–59)	Group 2 (60–69)	Group 3 (70–79)	Group 4 (80–89)
No. of cases ( $p < 0.001$ )	557	1745	1274	169
Age (years)	57	65	73	81
Volume (cm <sup>3</sup> ) ( $p = 0.003$ )	57	59	60	60
Surgery ( $p < 0.001$ ) (%)				
TURP	49.7	40.1	37.5%	47.9
OP	50.3	59.9	62.5	52.1
Inflammation ( $p = 0.817$ ) (%)				
Total	43.3	42.2	42.7	46.7
Chronic	29.1	31.0	29.4	26.6
Acute	14.2	11.2	13.3	20.1
Atrophy ( $p = 0.020$ )	2.3	4.1	4.9	5.3
PAH ( $p = 0.527$ )	1.3	1.1	1.6	0.6
AAH ( $p = 0.637$ )	4.1	4.7	4.6	4.1
PIN ( $p = 0.030$ ) (%)				
Total	1.2	1.9	2.8	3.5
LGPIN	0.5	0.9	1.6	1.2
HGPIN	0.7	1.0	1.2	2.3
Incidental carcinoma ( $p = 0.001$ ) (%)				
Total	3.0	4.8	7.6	10.1
T1a	2.9	4.2	6.4	6.5
T1b	0.1	0.6	1.2	3.6

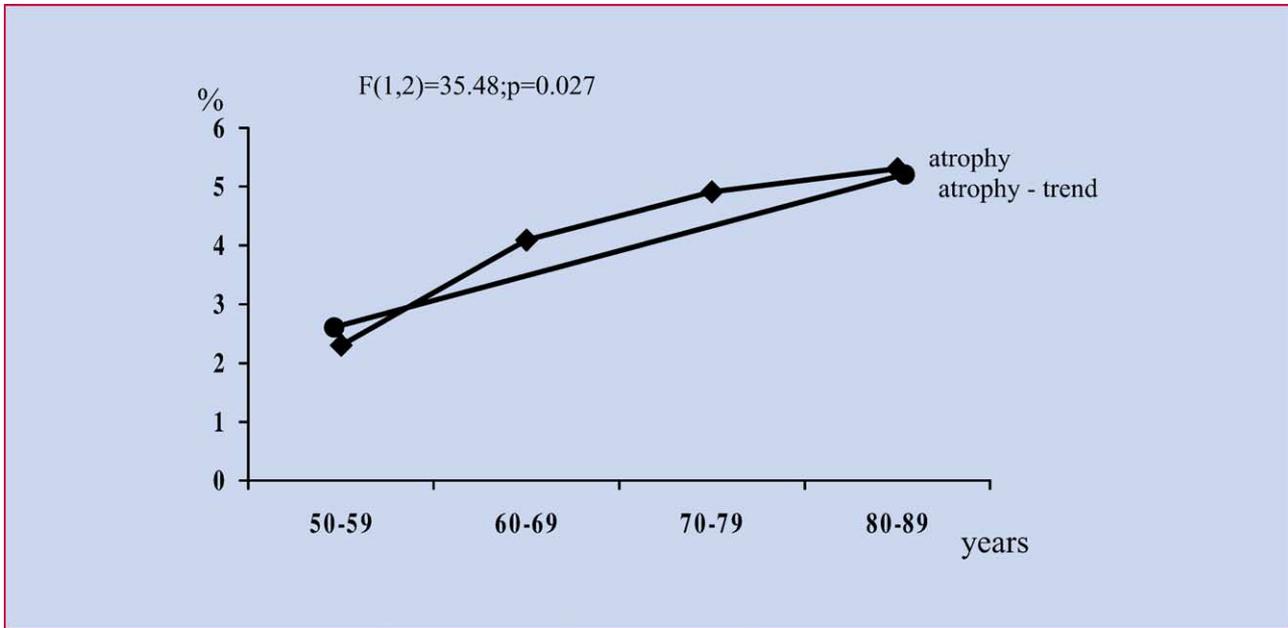


Fig. 1. Linear regression model (ANOVA): focal acinar atrophy trend according to the different decades of age.

The distribution of the other variables (inflammation, PAH, AAH) did not significantly vary according to patient decades of age (Table 3).

3.3. Results on the basis of prostate volume

In analyzing the subset of cases (2981) in which prostate volume measurement was available, most of our examinations were obtained from patients with prostate volume between 40 and 79 cc (90.5%).

The distribution of AAH significantly varied in the different groups ( $p = 0.003$ ) (Table 4), with a higher percentage in prostate volumes between 60 and 89 cc when compared with prostate volumes between 30 and 59 cc.

The distribution of inflammation significantly varied according to prostate volume ( $p < 0.001$ ) (Table 4), and regarding chronic inflammation, there was a trend to increase from group 1 to group 6 (Fig. 4).

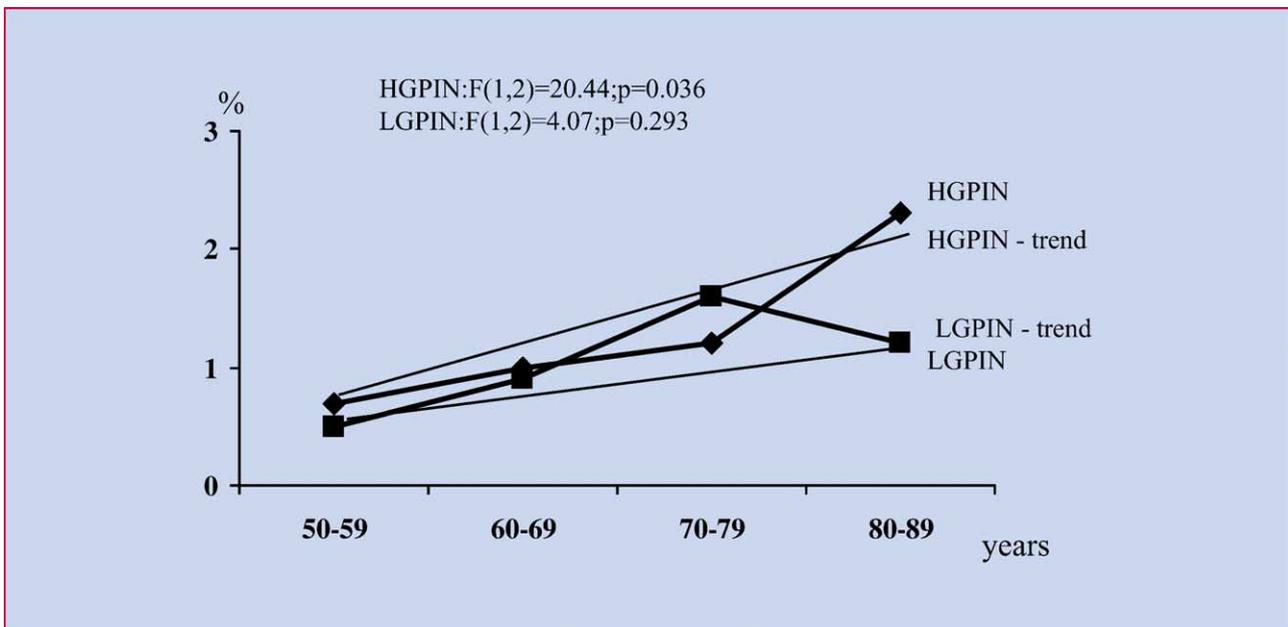


Fig. 2. Linear regression model (ANOVA): LGPIN and HGPIN trend according to the different decades of age.

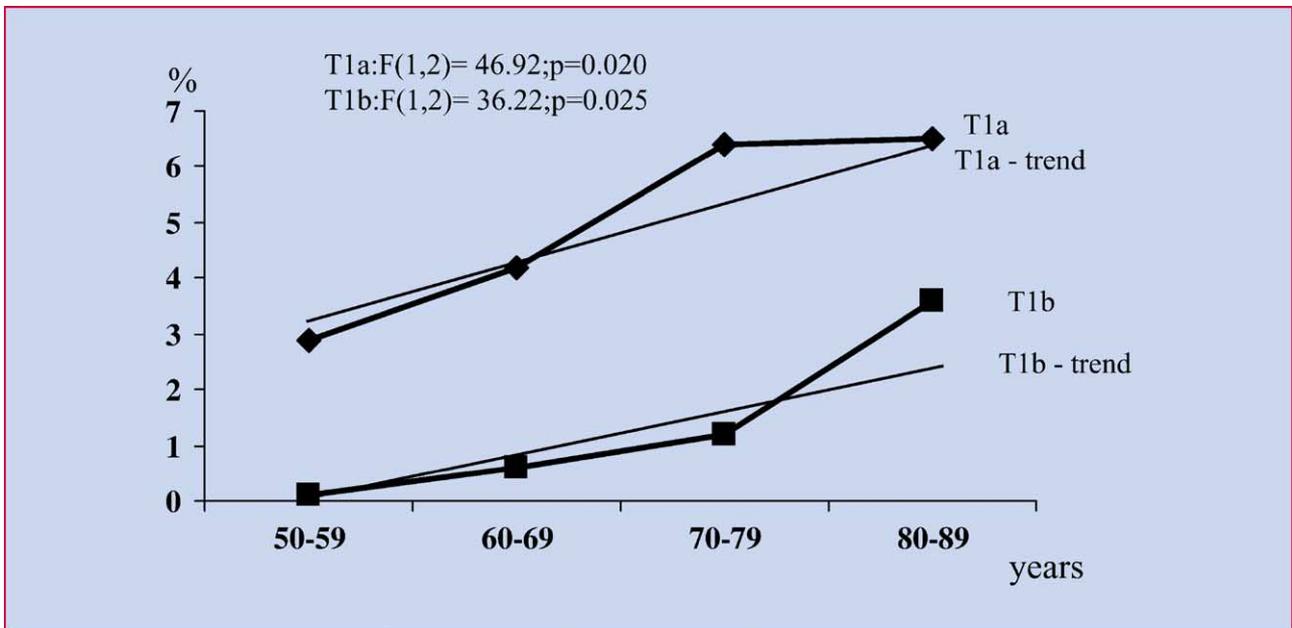


Fig. 3. Linear regression model (ANOVA): T1a and T1b trend according to the different decades of age.

In all groups, mild inflammatory aspects remained the most frequently found (group 1 = 76%; group 2 = 79%; group 3 = 83%; group 4 = 74%; group 5 = 78%; group 6 = 76%).

Using group 1 as the reference, patients in groups 2–6 were progressively more likely to present inflammation: group 2 versus group 1: odds ratio 1.69 (95% confidence interval 1.23–2.82); group 3 versus group 1:

**Table 4**

Distribution of the different variables according to prostate volume (cc)

Variable	Group 1 (30–39)	Group 2 (40–49)	Group 3 (50–59)	Group 4 (60–69)	Group 5 (70–79)	Group 6 (80–89)
No. of cases ( $p < 0.001$ )	142	713	555	764	667	140
Age (years) ( $p = 0.004$ )	66	66	66	68	68	68
Volume (cm <sup>3</sup> )	36	43	54	65	74	80
Surgery ( $p < 0.001$ ) (%)						
TURP	97.9	94.5	62.7	31.2	10.9	0
OP	2.1	5.5	37.3	68.8	89.1	100
Inflammation ( $p < 0.001$ ) (%)						
Total	17.6	29.9	37.3	50.0	55.0	77.8
Chronic	8.5	13.2	30.4	36.3	43.0	61.4
Acute	9.1	16.7	6.9	13.7	12.0	16.4
Atrophy ( $p = 0.662$ )	4.2	4.3	4.5	3.5	4.8	3.6
PAH ( $p = 0.830$ )	1.4	0.8	0.9	1.4	1.5	0.7
AAH ( $p = 0.003$ )	3.5	3.2	3.6	5.7	5.8	7.1
PIN ( $p = 0.060$ ) (%)						
Total	0	1.8	2.5	2.6	2.2	1.4
LGPIN	0	0.6	1.2	1.8	1.0	0
HGPIN	0	1.2	1.3	0.8	1.2	1.4
Incidental carcinoma ( $p = 0.060$ ) (%)						
Total	4.2	3.9	4.1	6.4	5.1	4.2
T1a	2.1	2.9	3.8	5.7	4.7	2.8
T1b	2.1	1.0	0.3	0.7	0.4	1.4

odds ratio 2.11 (95% confidence interval 1.34–3.20); group 4 versus group 1: odds ratio 2.84 (95% confidence interval 1.66–3.48); group 5 versus group 1: odds ratio 3.12 (95% confidence interval 2.12–4.43); group 6 versus group 1: 4.42 (95% confidence interval 3.15–5.48).

The distribution of the other variables (acinal atrophy, PAH, PIN, and incidental carcinoma) did not significantly vary according to prostate volume (Table 4).

### 3.4. Serum PSA level according to the histological diagnosis

In analyzing the subset of cases in which serum total PSA levels were available, all of our examinations were obtained from 1989 to 1998 (group 3 and group 4 according to the period of observation). For this analysis of PSA, we considered only BPH cases without or associated with only one of the histological variables that we included in the study. In these 2130 cases mean age was  $66.42 \pm 6.23$  (median 67) years and mean prostate volume was  $58.32 \pm 14.17$  cc (median 58 cc). Table 5 describes mean and median serum PSA levels and the percentage of cases with a PSA > 4.0 ng/ml, according to the histological diagnosis. The *p*-values were referred to differences in PSA levels between each histological group versus the group with only BPH. In our cases, the histological presence of inflammation (either chronic or acute), acinar atrophy, AAH, PIN (either LG or HG), T1a prostate cancer associated to BPH, was not able to significantly influence serum PSA levels when compared to cases with only histological BPH. Also classifying inflammation in mild, moderate and severe, this variable was not able to significantly modify serum PSA levels. The only one parameter able to significantly influence and significantly increase ( $p = 0.001$ ) serum PSA levels, was the presence of a T1b prostate cancer associated with the histological diagnosis of BPH. In particular, 90.4% of

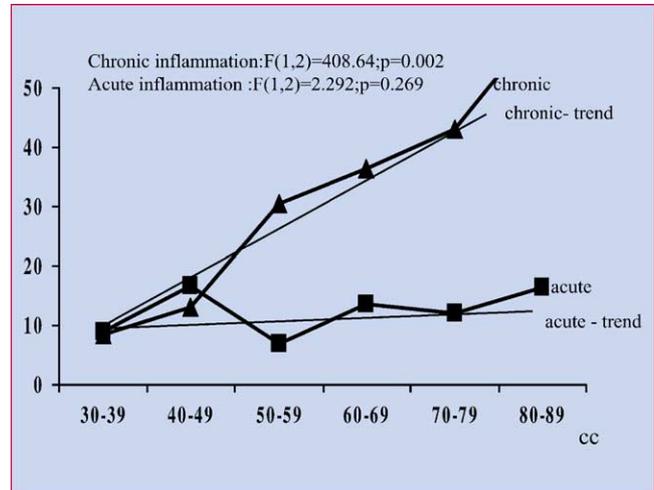


Fig. 4. Linear regression model (ANOVA): chronic and acute inflammation trend according to prostate volume.

cases with T1b prostate cancer presented serum PSA levels over 4.0 ng/ml, whereas the percentage of cases with >4.0 ng/ml serum PSA levels was lower and similar in all the other groups (inflammation, atrophy, AAH, PIN, T1a prostate cancer) and it was not significantly different to that of cases with only BPH. Moreover, similar results were obtained considering PSA density (total PSA/prostate volume PSAD). In fact, as for total PSA levels, the histological presence of inflammation, atrophy, AAH, PIN, T1a associated to BPH, was not able to significantly ( $p > 0.05$ ) influence PSAD when compared to cases with only histological BPH. On the contrary the only parameter able to significantly ( $p = 0.001$ ) influence PSAD was the presence of a T1b prostate cancer. In particular 90.4% of cases with T1b prostate cancer presented a PSAD > 0.15, whereas the percentage of cases with >0.15 PSAD was lower than 60% in all other groups and it was not significantly different to that of cases with only BPH.

**Table 5**

Mean  $\pm$  S.D. (median) serum PSA levels according to the different histological groups

Histological group	No. of cases	Total PSA (ng/ml)	<i>p</i> -value (vs. only BPH)	Percentage of cases (PSA >4 ng/ml)
BPH alone	743	5.1 $\pm$ 2.8 (5.0)		65.0
Chronic inflammation	721	5.2 $\pm$ 3.1 (5.5)	0.517	68.6
Acute inflammation	215	5.4 $\pm$ 2.1 (5.2)	0.146	69.3
Focal atrophy	98	5.1 $\pm$ 1.8 (5.0)	0.945	63.2
PAH	39	4.7 $\pm$ 1.3 (5.0)	0.376	58.9
AAH	112	5.2 $\pm$ 2.3 (5.3)	0.719	64.2
LGPIN	19	4.6 $\pm$ 1.3 (5.0)	0.438	57.3
HGPIN	31	5.9 $\pm$ 2.3 (5.5)	0.117	67.7
T1a	131	4.9 $\pm$ 2.1 (5.2)	0.436	62.5
T1b	21	7.9 $\pm$ 2.2 (7.5)	0.001	90.4

*p*-values are referred to differences in PSA levels between each histological group vs. the group with only BPH.

In these 2130 cases, serum PSA levels were significantly associated with the age of patients ( $r = 0.3226$ ,  $p < 0.001$ ) and with prostate volume ( $r = 0.3329$ ,  $p < 0.001$ ). This correlation was significant regardless of whether BPH was associated or not with inflammation, acinar atrophy, AAH, PIN and T1a prostate cancer. In general, in all these groups, median serum PSA value increased with age decades and prostate volume. On the contrary, no significant association between PSA and age ( $r = 0.1216$ ,  $p = 0.127$ ) or PSA and prostate volume ( $r = 0.0825$ ,  $p = 0.376$ ) was found in the group of cases with T1b prostate cancer.

#### 4. Discussion

In this study we used the histopathological examinations performed by the same pathologist over a 20-year period to describe some aspects which can be associated with the histological diagnosis of BPH, in relation to clinical parameters such as patient age, prostate volume, and different periods of observation. Moreover we analyzed the influence of these different histological aspects on serum PSA levels.

The strengths of this study were the relatively large sample size and the standardized review of pathological materials.

Our results cannot be referred to a global population of BPH cases, but they are restricted to BPH cases admitted to surgery. The number of histological examinations for BPH significantly increased from 1979 to 1998. This finding confirms in part that despite the introduction of alternative strategies to treat BPH patients in our clinic, surgery continues to be performed as a primary treatment or after failure of a previous non-surgical treatment for BPH. However, the increase in the number of cases is associated with a global increase of the number of patients with BPH who were diagnosed and evaluated in our clinic from 1979 to 1998, rather than a simple increase in the indication for surgery or a late diagnosis of BPH.

In our analysis we considered a clinical parameter such as prostate volume and not a histological parameter such as resected prostate weight for two main reasons. We obtained the resected prostate weight in only a very limited number of cases. Prostate size and weight at BPH surgery were not systematically measured in vivo. On the contrary, prostate volume in 2984 cases was homogeneously measured preoperatively by TRUS [12]. Moreover, it may be more relevant to associate histological results obtained only after surgery with a clinical parameter that can also be obtained prior to surgery. Several studies attempted to correlate

histological findings to prostate volume variations in BPH patients [23]. The correlation between calculated prostate volume and resected prostate weight, when using TRUS, ranges from 0.78 to 0.94 using standard methods [24]. Comparison of predicted volume with tissue removed by TURP is fraught with difficulties, including the water loss of the chips, tissue destruction, incomplete resection etc. [25]. Transitional zone volume measured by TRUS seems to be more related to surgically resected prostate weight [26], but the introduction of this parameter is relatively new, and in our population, it was measured only in very few cases.

Many of our examinations were obtained from open suprapubic prostatectomy. Up to 20 years ago, open surgery was the most common approach, and especially in some urology clinics of Italy, open prostatectomy remained the principal surgical approach for BPH for a long time even after endoscopic methodologies were introduced [27].

The first histological variable we considered is inflammation. It is well recognized that BPH and inflammation can coexist in the prostate, but the interrelationship between BPH and histologically defined prostatic inflammation is not well known [4]. Gleason [28] and Kessler [29] suggested that immunoinflammatory stimulators might play a role in the prostatic epithelial cell growth by modulating the cytokine system and might promote hyperplastic changes. Histological evidence of prostatic inflammation is often present in biopsy, surgical and autopsy material [4]. Nickel et al. [4] on histological sections obtained from 80 patients submitted to TURP for BPH showed that inflammation was identified in all patients, but the mean tissue surface area involved was only 1.1% of the total specimen. Anjun et al. [20] reported that histological evidence of prostatic chronic inflammation was present in about 50% of cases submitted to TURP for BPH. In our analysis, inflammatory aspects were associated to BPH in a high percentage (43.1% = 1700 cases) of cases, predominantly as chronic (69% of 1700 cases) and mild (78%) inflammation. We did not find significant differences in the percentage and categorical distribution of inflammatory aspects according to the different decades of age of patients. On the contrary, inflammation, particularly in the chronic form, significantly increased with the increase in prostate volume but remained predominantly mild.

The second histological aspect that we considered was the presence of AAH in our BPH specimens. In contrast with HGPIN, most of AAH (86%) are localized in the transition zone of the prostate and no evidence of a direct transition from AAH to cancer has been demonstrated [10,30]. Some authors [16,30]

have suggested that AAH may be the precursor to the transition zone well differentiated carcinoma. The incidence of AAH in TURP material varies between 4 and 15% [31]. Little is known about the age-dependent frequency of AAH and usually, AAH is diagnosed in TURP specimens of patients with a mean age of more than 60 years [31]. In our analysis, we did not find significant differences in the distribution of AAH depending on the patient's decade of age. On the contrary, the distribution of AAH significantly varied depending on prostate volume ( $p = 0.003$ ), particularly with a higher percentage in prostate volumes between 60 and 89 cc when compared with lower prostate volumes.

Another aspect that we considered in our histological samples was the presence of focal acinar atrophy. Diffuse atrophy in the prostate may result from a decrease in circulating androgens and involved the entire prostate gland in a relatively uniform manner [8]. In contrast, focal atrophy is not related to decreased circulating androgens and it occurs as patches of atrophic epithelium within a background of surrounding normal-appearing non-atrophic epithelium [8]. In elderly patients, atrophic glands, which sometimes show cystic dilatation, can be found in transurethral resection material from the transition zone of the prostate [31]. In 1935 Moore [32] pointed out that prostate carcinoma is often associated with glandular atrophy. More recently, other authors have suggested a relationship between glandular atrophy and PIN [8,33]. Putzi and Marzo [33] showed that simple atrophy and PAH prostatic lesions often merge directly with HGPIN (34% of atrophic lesions). The same author, however, affirmed that focal atrophy of the prostate and PAH are also often associated with chronic and, less frequently, acute inflammation [33]. However, in the WHO Consensus Conference of Stockholm [30], it was emphasized that no relationship between atrophy and prostate carcinoma or HGPIN has been proved.

In our population, we found a relatively low percentage (4.2%) of examinations showing focal glandular atrophy. In consideration of this low percentage, we could not classify these atrophic lesions on the basis of the number or extension, and correlations with the other histological variables considered (inflammation, PIN, AAH and IC) were all weak. In our experience, the distribution of acinar atrophy significantly varied depending on patient age ( $p = 0.020$ ), and there was a trend to increase with decades of age. On the contrary, distribution of acinar atrophy was not influenced by prostate volume ( $p = 0.662$ ).

The clinical significance of HGPIN as a pre-malignant lesion for prostate cancer has been well accepted;

on the contrary, according to the consensus conference [30], LGPIN is regarded as having no diagnostic or therapeutic significance. McNeal and Bostwick underlined that PIN and prostate cancer are both age-associated lesions [34]. The prevalence of PIN varies significantly depending upon the type of prostate tissue sample, the cohort studied, diagnostic criteria, racial, and age distribution [35]. The Wayne State University study revealed data on the age and racial distribution of PIN [36]. A higher prevalence of HGPIN in African-American men was found compared to that in Caucasian men and was found to increase with age. Other studies suggest that LGPIN first emerges in men in the third decade of life [37,38].

The second aspect that influences PIN incidence is the type of prostate tissue sample. The occurrence of PIN in TURP specimens is relatively uncommon (2–4%), confirming that PIN is predominantly localized in the peripheral zone of the prostate gland.

In our analysis the lower percentage (1.7%) of PIN diagnosed from 1979 to 1988 when compared to 1989–1998 (2.3%) may be partly associated with a significantly lower number of examinations obtained in the first period. We found a significant trend to increase with age decades ( $p = 0.036$ ) in regard to HGPIN. Using as a reference the patients in the fifth decade of age, patients in the sixth, seventh and eighth decades of age were progressively more likely to have HGPIN.

The last aspect that we considered was the diagnosis of incidental carcinoma of the prostate in our BPH specimens. In prior studies, approximately 16% of TURP for BPH revealed incidental carcinoma of the prostate [39,40]. Currently, fewer cancers are incidentally detected on TURP compared to a few years ago. Tombal [40] described that T1 disease decreased from 23% to 7% between 1985 and 1997; this decrease was marked for stage T1b, which declined from 18% to 2% unlike the incidence of stage T1a which remained constant. The reduction of incidentally TURP detected cancers may be due to a combination of factors: the introduction of medical therapies for the treatment of BPH, the introduction of alternative treatment options that do not provide tissue for the histological examination, and the introduction of PSA in the diagnostic evaluation of patients may partly explain this reduction. Anderson et al. [39] reviewed all pathological records of TURP specimens taken between 1980 and 1989. The likelihood of finding incidental prostate cancer on TURP varies with age, especially for T1b cancers.

We found incidental carcinomas in only 5.5% of our examinations for BPH.

In particular, we found a very low percentage of T1b carcinomas (0.8%) rather than T1a (4.7%). As has also

been shown by other authors [40], no T1a cases presented a Gleason score of 7 or more. During our study period of 20 years, the percentage of incidental carcinoma varied in the different periods of observation but, unlike other reports [40], we did not find a specific trend to decrease over time. As found in other experiences [39,40], there was a trend for incidental carcinoma (both T1a and T1b) to increase with patient age.

If we consider together all histopathological aspects that we included in our analysis (inflammation, AAH, atrophy, PIN, IC), it is important to underline that, in analyzing for a correlation between the different histological variables, all associations were found to be very weak and not statistically significant.

In our analysis we tried to study the relationship of some histological variables associated to BPH with some clinical parameters such as age of the patient and prostate volume. We emphasize that, in our cases, the distribution of acinar atrophy, such as that of HGPIN and IC, significantly increased according to patient decade of age, but it did not significantly vary depending on prostate volume; on the contrary, AAH, such as in inflammation associated with BPH, significantly varied depending on prostate volume but not on patient age. It is possible, therefore, that histological aspects such as acinar atrophy, PIN and prostate carcinoma that are more frequently localized in the peripheral zone of the prostate [31,35], are significantly influenced by patient age but not by prostate volume modifications. On the contrary, aspects such as inflammation and AAH that are more frequently localized in the transition zone of the prostate [4,31], are significantly influenced by prostate volume but not by patient age variability. However, the relatively low number of patients in whom some of these variables were diagnosed, may in part limit the significance of these data. Moreover, we must remember that our samples are limited to BPH patients admitted to surgery.

We also tried to analyze the influence of these histological variables on serum PSA levels. Unfortunately we obtained data on PSA only in cases from 1989 to 1998 and in some histological groups the number of cases was low, which in part reduces the significance of our results regarding PSA variable. In our BPH cases, serum PSA levels were significantly influenced by the presence of T1b prostate cancer but not by the presence of histologically proved inflammation, acinar atrophy, AAH, PIN and T1a prostate cancer. Similarly the relationship between PSA and prostate volume and PSA and age became not significant only in cases with T1b prostate cancer associated with BPH but it was not influenced by the presence of the other histological variables. There is almost general consensus concerning the effect of prostate size and age on PSA levels [41]. Also Morote et al. [42] underlined that inflammation has an important prevalence in prostate specimens but it seems to have no significant influence on serum PSA levels. Similarly PIN does not appear to elevate the prostatic serum antigen [30,35]. However, some authors showed that PIN cases at surgery for BPH have PSA levels intermediate between those found in prostate cancer and BPH [43]. Tombal et al. [40] assessing the relationship between serum PSA and incidental prostate cancer in patients submitted to surgery for BPH, showed that 70% of the incidental tumors associated with a PSA levels >4.0 ng/ml were T1b and more than half of the patients with T1a tumors had a PSA level of <4 ng/ml.

The histopathological analysis of BPH is very complex. Only a complete description obtained from the examination of prostate tissue specimens can help the clinician in the management of the single patient with BPH. Different clinical aspects can be significantly related to the histological diagnosis of BPH. A combined histological and clinical analysis can reveal important associations also in this disease.

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