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Prevalence of latent prostate cancer and prostatic intraepithelial neoplasia in İstanbul, Turkey: an autopsy study

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Aim: To investigate the frequency of latent prostatic carcinoma (PCa) and prostatic intraepithelial neoplasia (PIN) in the Turkish population.

Materials and methods: PCa and PIN were evaluated in 116 male autopsy cases in which the cause of death was nontumoral. All patients were Turkish, living in İstanbul, and aged 40-79 years.

Results: The prevalence of PCa was 19.8% and the decade rates (decades 5-8) were 9.5%, 12.5%, 18.8%, and 37%, respectively ($P < 0.011$). The rates of high-grade prostatic intraepithelial neoplasia (HGPIN) were 33.3%, 31.3%, 56.3%, and 25.9% for decades 5-8, respectively ($P > 0.05$). A total of 68.4% of PCa cases were HGPIN. There was a statistically significant correlation among HGPIN, PCa, and Gleason scores ($P < 0.002$).

Conclusion: The prevalence of latent PCa in the Turkish population is very high (19.7%). In order to determine latent PCa cases, males over 40 years of age must be screened more strictly.

Key words: Prostate cancer, prostatic intraepithelial neoplasia, prevalence, Turkish males, autopsy

Türkiye, İstanbul'da latent prostat kanseri ve prostatik intraepitelyal neoplazinin sıklığı: Otopsi çalışması

Amaç: Türk toplumunda latent prostat kanseri (PCa) ve prostatic intraepitelyal neoplazi (PIN) sıklığını araştırmayı amaçladık.

Yöntem ve gereç: Tümör dışı nedenler ile ölen 116 erkek otopsi olgusunda alınan prostat dokularında PCa ve PIN değerlendirildi. Olguların hepsi İstanbul'da yaşayan Türk vatandaşlarından oluşuyordu ve yaşları 40-79 arasında değişmekte idi.

Bulgular: Tüm olguların % 19,8'inde PCa saptandı ve bunların dekatlara (5.-8.) göre dağılımı sırasıyla % 9,5, % 12,5, % 18,8 ve % 37'dir ($P < 0,011$). Yüksek dereceli (HG) PIN oranı dekatlara (5.-8.) dağılımı sırasıyla, % 33,3, % 31,3, % 56,3 and % 25,9'dur. PCa olgularının % 68,4'ünde eş zamanlı olarak HGPIN de saptandı. HGPIN ile PCa ve Gleason skoru arasında istatistiksel olarak anlamlı ilişki saptandı ($P < 0,002$).

Sonuç: Türk toplumunda latent PCa sıklığı yüksek oranda (% 19,7)'dır. Latent PCa olgularını saptamak için, 40 yaş üstü erkeklerin daha sıkı taranması gereklidir.

Anahtar sözcükler: Prostat kanseri, prostatik intraepitelyal neoplazi, prevalans, Türk erkekleri, otopsi

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Introduction

Prostatic carcinoma (PCa) is a public health problem that is currently the most common neoplasm and the second leading cause of cancer-related deaths in males of western populations. Although it is more commonly seen in males aged 64 and over, there has been an increase in the frequency of PCa in people under 50 years of age in recent years. This increase has been attributed to a western-type diet and widespread screening programs (1-6).

High-grade prostatic intraepithelial neoplasia (HGPIN) is now accepted as the most likely preinvasive stage of adenocarcinoma. Prostatic intraepithelial neoplasia (PIN) has a high predictive value as a marker for adenocarcinoma, and its identification warrants repeat biopsy for concurrent or subsequent invasive carcinoma. The only method of detection is biopsy; PIN does not significantly elevate serum prostate-specific antigen (PSA) concentration or its derivatives, and it cannot be detected by ultrasound. Most studies suggest that most patients with PIN will develop carcinoma within 10 years (7-13).

PCa starts silently and may not be noticed until the postmortem examination. The term "latent PCa" is used to define PCa that is clinically silent and determined during postmortem examination. "Unsuspected" or "incidental PCa" refers to PCa cases showing no abnormalities in the digital rectal examination (DRE), routine PSA analysis, or transrectal ultrasonography (5). Latent PCa cases are found in autopsies (11,14-18), and unsuspected PCa cases are generally incidentally detected in the specimens of radical cystoprostatectomy (RCP) (19-25) performed for bladder cancer or in the specimens of prostatectomy and transurethral resection (TUR) performed for nodular hyperplasia.

The majority of the epidemiologic studies related to PCa and PIN are based on the biopsy outcomes obtained from symptomatic patients and PSA screenings (2,3,26,27). The specificity and sensitivity of these studies in showing the prevalence of PCa is lower than those of autopsy studies (3,5,28-30). Therefore, it is thought that an important group is present in the population (40%-46%) with undiagnosed, clinically silent pathologies of the prostatic gland. These cases are incidentally detected, and the frequency of these lesions differs by population (11,15-22).

There is currently no study about the prevalence of latent PCa in the Turkish population in either the English or Turkish literature. The current study is the first of its type. The aim of this study was to assess the prevalence of latent PCa and PIN, their ranges within decades, and their relationship with Gleason score.

Materials and methods

We examined prostate glands obtained from the autopsies of 116 consecutive Turkish men, whose autopsies were carried out at the Institute of Forensic Medicine, İstanbul. In none of these 116 cases was the cause of death cancer-related (Table 1). All prostate glands were removed with the seminal vesicle and

Table 1. Causes of death in the studied cases.

Cause of death	n	%
Cardiovascular disease	35	36.5
Transportation fatalities	13	13.5
CO intoxication	7	7.3
Firearm fatalities	7	7.3
Mechanical asphyxia due to hanging	5	5.2
Respiratory failure resulting from pneumonia	4	4.2
Fall from great heights	4	4.2
Drowning	3	3.1
Work-related fatalities	3	3.1
Posttraumatic fat embolism	3	3.1
Blunt cranial trauma	3	3.1
Suicide by jumping from a bridge	2	2.1
Intracerebral bleeding (nontraumatic)	1	1.0
Mushroom poisoning	1	1.0
Complications related to cirrhosis	1	1.0
Tuberculosis	1	1.0
Stab wounds	1	1.0
Meningitis	1	1.0
Heroin intoxication	1	1.0
Total	**96**	**100**

fixed in 10% neutral buffered formaldehyde. Of these 116 cases, 20 were excluded from the study due to lack of clinical information and/or fixation error.

During the macroscopic examination, specimens of prostate were cut into sections at intervals of 0.5 cm, and the cut surfaces were examined. A total of 7-11 specimens (average: 9) were taken from every gland. All of the blocks obtained were embedded in paraffin, sectioned to produce 5-µm whole-mount sections, and stained with hematoxylin and eosin. During the microscopic examination, specimens were analyzed for the presence of PCa and PIN. Gleason scoring was used to grade the PCa. PIN cases were subdivided into categories of low grade or high grade.

For statistical evaluation, the range of PCa according to decade and the relationship between PIN and Gleason score were calculated by the Pearson correlation method using SPSS 12.0.

Results

The age distribution of the patients ranged between 40 and 79 (mean: 59.6, median: 58). The number of patients in decades 5-8 was 21, 32, 16, and 27, respectively. Of these patients, 21.8% were under 50, 41.7% were between 50 and 65, and 36.5% were over 65 years old.

PCa was detected in 19 (19.8%) of a total 96 cases. The prevalence of PCa by decade was 9.5%, 12.5%, 18.8%, and 37%, respectively, for decades 5-8 ($P < 0.011$) (Table 2, Figure 1). A linear relationship was found between PCa and decade (Figure 2). The patients were grouped as follows: under 50, 50-65, and over 65 years old. PCa was detected in 9.5% of patients under 50 years of age, 15% of patients aged 50-65, and 31.4% of patients over 65. Among the PCa cases, 2 patients were under 50 years of age (10.5%), 6 patients (31.6%) were between 50 and 65, and 11 patients (57.9%) were over 65 years. Of the 19 PCa cases detected, 11 (58%) were well differentiated and 8 (42%) were moderately differentiated. There were no poorly differentiated PCa cases in this series.

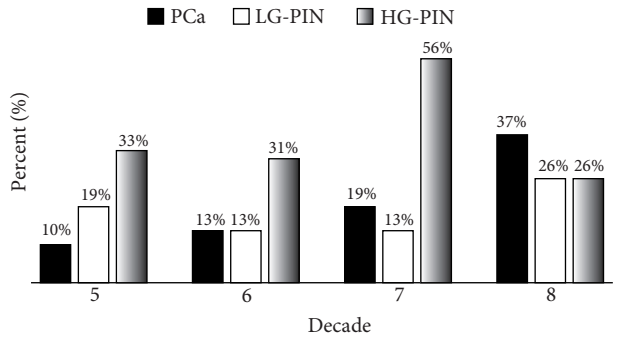

Figure 1. Percentage of prostate carcinoma [PCa] cases and low-grade and high-grade prostatic intraepithelial neoplasia (LGPIN and HGPIN, respectively) by decade.

PIN was detected in 50 cases (52%). Of these PIN cases, 33 (34.4%) were HGPIN and 17 (17.7%) were low-grade prostatic intraepithelial neoplasia (LGPIN). The frequency of HGPIN by decade was 33%, 31%, 56%, and 26%, respectively, for decades 5-8 (Figure 1). Relatively more cases of HGPIN were found in decades 7 and 8 (Table 2). There was no statistically significant relationship between HGPIN and LGPIN by decade ($P > 0.05$).

PIN was detected in 14 out of a total of 19 PCa cases (74%). Of these cases, 13 (93%) were HGPIN. PIN was detected in 36 (47%) of a total 77 nodular

Table 2. Range of PCa and PIN according to decades.

	Decades				Total	P-value
	5 (%)	6 (%)	7 (%)	8 (%)		
n	21	32	16	27	96	
PCa	2 (9.5)	4 (12.5)	3 (18.8)	10 (37)	19	0.009
LGPIN	4 (19)	4 (12.5)	2 (12.5)	7 (25.9)	17	0.176
HGPIN	7 (33.3)	10 (31.3)	9 (56.3)	7 (25.9)	33	0.911

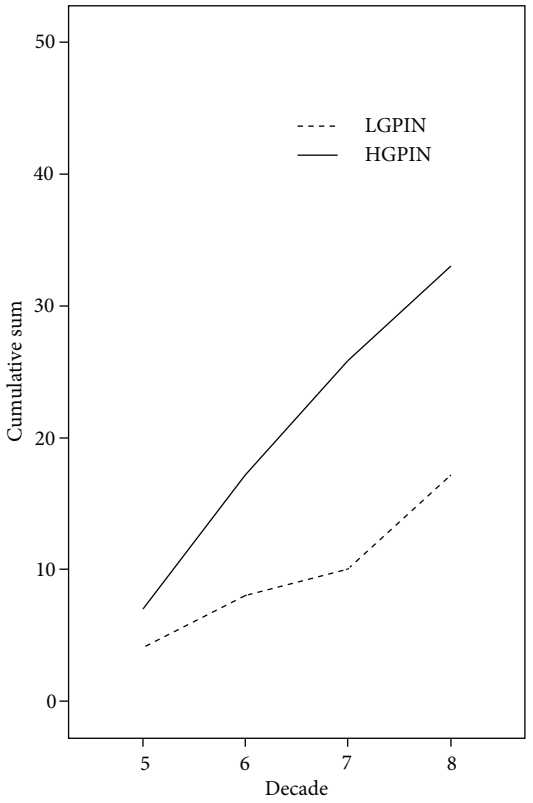

Figure 2. Cumulative frequency of PCa and PIN by decade.

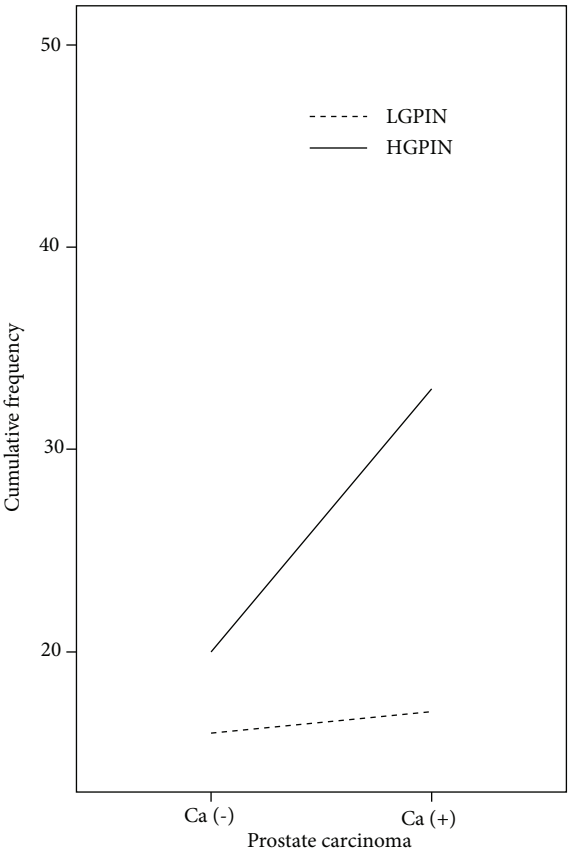

Figure 3. The linear relation between PCa and LGPIN and HGPIN.

hyperplasia cases, and, among these PIN cases, 20 (26%) were HGPIN and 16 (21%) were LGPIN. Linear relationships among the PIN, PCa, and Gleason score were found (Figures 3 and 4). Although there was a statistically highly significant correlation of HGPIN with PCa and Gleason score ($P < 0.002$), it was not significant in terms of the relation to decade ($P > 0.05$). There was a strong negative correlation between HGPIN and nodular hyperplasia ($P < 0.006$).

Discussion

Prostate cancer is the second most frequently diagnosed cancer in men (903,000 new cases, 13.6% of the total) and the fifth most common cancer overall. Nearly three-fourths of the registered cases occur in developed countries (648,000 cases). Incidence rates of prostate cancer vary by more than 25-fold worldwide; the highest rates are in Australia and New Zealand (104.2 per 100,000), western and northern Europe, and North America. Incidence rates are also relatively high in certain developing regions such as the Caribbean, South America, and sub-Saharan Africa. The lowest age-standardized incidence rate (ASR) is estimated to be that of south-central Asia (4.1 per 100,000). Turkey belongs to the group of low-incidence (14.8 per 100,000) countries. The difference between high- and low-incidence regions varies between 30-fold and 400-fold (31).

With an estimated 258,000 deaths in 2008, prostate cancer is the sixth leading cause of cancer death in men (6.1% of the total). Because PSA testing has a much greater impact on incidence than on mortality, there is less variation in mortality rates worldwide (10-fold) than in incidence rates (25-fold), and the number of deaths from prostate cancer is almost the same in developed and developing regions. Mortality rates are generally high in predominantly black populations (Caribbean, ASR of 26.3 per 100,000; sub-Saharan Africa, ASR of 18-19 per 100,000), very low in Asia (ASR of 2.5 per 100,000 in eastern Asia, for example), and intermediate in Europe and Oceania (31).

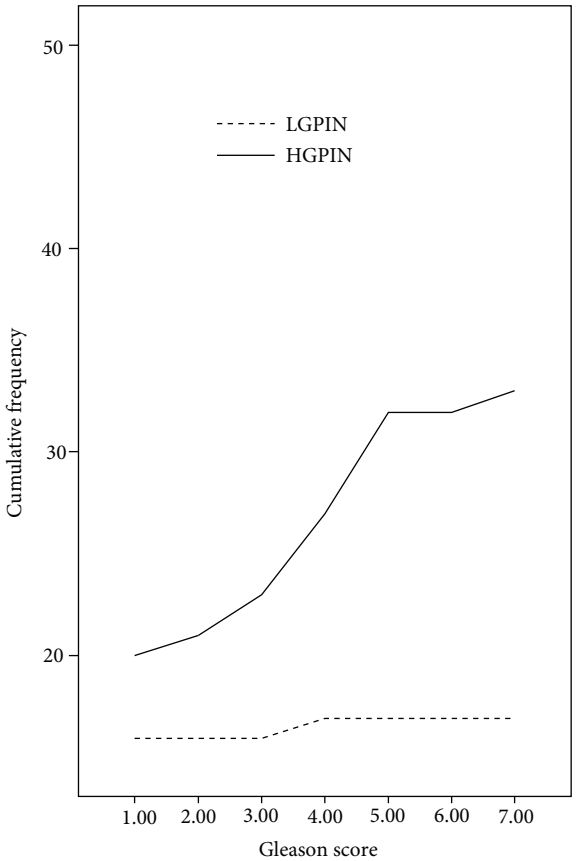

Figure 4. Cumulative frequency of LGPIN and HGPIN by Gleason scor

Migration studies show that men moving from Japan and China to the US adopt an increased risk of prostate cancer. Second and third-generation Japanese Americans and Chinese Americans actually have a prostate cancer risk level similar to that of white American men. This suggests that environment has an influence on prostate cancer (5,32).

The geographical distribution of PCa differs, and, even within the same country, there is a significant difference in terms of incidence and mortality in individuals of different races. PCa is seen more frequently (2-fold) in blacks than whites, and the mortality rate is also higher among blacks (1-5,31-33).

It has been reported that there has been a significant increase in the incidence of PCa worldwide in the past 30 years (2-5,29,33-35). This increase is attributed to the widespread use of PSA screenings, the aging of the population, and excessive caloric intake. Widespread use of PSA screening has resulted in the detection of PCa cases in the early stages. As a result of the above factors, an increase in radical prostatectomy cases of up to 40% and an increase in tumors of T1 grade in individuals younger than 60 have been reported (3,5,29,33-36).

In autopsy and RCP studies, PCa that is clinically silent and undetected in routine screenings has been found at high rates. Although the PCa rates detected in these studies differ, the outcomes of RCP cases are higher than those of autopsy cases. The frequency of PCa in autopsy studies was reported to range between 18% and 39% (average: 27%) (11,14-18); it ranged between 4% and 70% (average: 34%) in RCP studies (19-25,37,38). The frequency of incidentally discovered PCa in cystoprostatectomy specimens is extremely variable because of several factors, particularly the pathology sampling. The rate of clinically detectable PCa in men with bladder cancer was 19-fold greater than expected. It has been proposed that the high incidence of prostate and bladder cancer occurring together can be explained by a common carcinogenic pathway (19-24). Kurokawa et al. (37) reported that the detection rate of PCa was 12.5% and 1.5% in bladder cancer cases and control cohorts, respectively. This finding shows that PCa incidence studies carried out in RCP cases may be misleading for detection of PCa incidence. For this reason, PCa data obtained from autopsy studies become more important.

Stemmermann et al. (15) reported prostate cancer in 27% of autopsied Hawaiian Japanese men who died after 50 years of age, reaching a frequency of 63% among men over 80 years of age. The volume of 60% of these cancers was less than 150 mm^3. These small tumors would probably not have been discovered in a screening program. Tumors larger than 1000 mm^3 would probably have been discovered using modern diagnostic procedures, but were found in only 4.4% of the autopsied men. These data show that there is a significant difference between the incidence of PCa detected in the community and the real incidence of PCa (38).

Although PCa is commonly seen in men over 65 years of age, the increase in the number of cases in those under 50 years of age in recent years is striking. The incidence of PCa increases with age in a linear

manner (3-5,10-12,14,29,30). PCa is diagnosed in 30% of men in decade 4 of life, in 50% of those under 50 years old, and in 75% of those over 85 years old. Familial PCa cases generally emerge at earlier ages (1,4).

In an autopsy study carried out in Spain, Sanchez-Chapado et al. (14) reported the prevalence of PCa as 3.58%, 8.82%, 14.28%, 23.8%, 31.7%, and 33.33% in decades 3-8, respectively. In our study, the prevalence of PCa was 9.5%, 12.5%, 19%, and 37% in decades 5-8, respectively. The prevalence of PCa in decades 6 and 7 in the Spanish population was approximately 2 times higher than in the population from our study. However, the prevalence rate in decade 8 was slightly higher in our population (37%).

The incidence of HGPIN ranges between 29% and 85% in different studies. The most important reason for this great variation is the fact that HGPIN rates differ in different populations (8,10,11,14,39). Desai et al. (8), Fujita et al. (39), and Sanchez-Chapado et al. (14) reported rates of HGPIN at 85%, 51%, and 29% in India, Japan, and Spain, respectively. Our study found a rate of 34% in the Turkish population.

While the coincidence of HGPIN with nodular hyperplasia is 4%-18%, the coincidence of HGPIN and PCa ranges between 33% and 100% (average: 70%) (8,11,14,21,25,26,30). In this study, we detected HGPIN in 68.4% of PCa cases and 26% of nodular hyperplasia cases. There was a statistically significant correlation between HGPIN and PCa ($P < 0.002$).

The distribution and/or extent of HGPIN correlates with the age of the patient, prostate cancer stage, and grade and volume (9,10). Sanchez-Chapado et al. (14) reported a statistically significant association between tumor dimension and pathologic stage, but they found no such association among PSA level, Gleason score, and patient age. We found a statistically significant association between HGPIN and tumor grade ($P = 0.002$), but not with age ($P > 0.05$).

HGPIN prevalence differs in different racial groups living in the same country. In the US, the prevalence of HGPIN in blacks is 2 times higher than that in whites, just as with PCa (10). Sakr et al. (12) found that HGPIN starts in young individuals and increases progressively with advancing age in both whites and blacks, but is more prevalent in African Americans. Additionally, the more extensive form of HGPIN, with multifocal or diffuse involvement of the gland, appears at a younger age in African Americans. The finding that HGPIN is more prevalent in African Americans and that the more diffuse form appears earlier in this same group indicates a potentially important role for this lesion in the race-related discrepancies associated with this disease.

The frequency of poorly differentiated tumors has decreased due to an increase in the number of cases diagnosed early. Perotti et al. (36), comparing US data from 1980-1984 and 1990-1994, reported a decrease in the number of grade 3 PCa cases (24.4% versus 21.4%), a decrease in metastasis rates (33.1% versus 17.4%), and an increase in the number of patients undergoing radical prostatectomy or radiotherapy.

Frequency of PCa increased with increasing age, but the mortality rate was inversely related to age, as indicated by 30% mortality in those younger than 60 years old, 24% in those between 60 and 70 years old, and 7.5% in those over 70 years. Among those with carcinoma, 83% died of other unrelated causes; of those who died, 80% had poorly differentiated (grade 3 or 4) tumors. Given the indolent biological nature of well-differentiated tumors in those older than 70 years, PCa should not, in most instances, be regarded as a life-threatening diagnosis, with or without treatment, in older individuals. The tumor seems to be biologically more aggressive in younger men, especially those younger than 60 years (16).

In conclusion, autopsy studies show that, despite the widespread use of screening programs, there is still an asymptomatic PCa group in the community at a rate of 20%-26%. The current screening programs must be used more, and the diagnostic methods must be further developed in order to detect this patient group. The strong correlation between HGPIN and PCa confirms these lesions as a preinvasive stage of PCa.

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