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Frequency of high-grade prostatic intraepithelial neoplasia in Mexican population

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ABSTRACT

Background. High-grade intraepithelial neoplasia (HGPIN) is the only lesion regarded as precursor of prostatic carcinoma, though its frequency is unknown in many countries. Here we studied the frequency of HGPIN in a population with high grade frequency of prostatic carcinoma. **Material and methods.** A total of 486 cases of sextant prostatic biopsies performed from January 2001 to January 2006 were reviewed. These included 280 biopsies from patients belonging to an urban population, with medium or high socioeconomic status, from two hospitals in Mexico City. For comparison, 206 cases from the Regional Hospital of Tabasco located in the tropical zone of the country were included. This hospital receives patients from a rural population with low income and socioeconomic status. **Results.** Of the total 486 cases, 162 (33.33%) cases were diagnosed as prostatic carcinoma and 319 (65.64%) as benign conditions. Only in five (1.03%) biopsies was HGPIN found. Three of these patients were from Mexico City, and two from the Regional Hospital of Tabasco. **Conclusions.** Even when our results were obtained only in three hospitals, they suggest that a low frequency of HGPIN on needle prostate biopsies does not necessarily mean a low frequency of prostatic carcinoma in the same population. The reason for such a disparity could be related to a reduced extension of HGPIN areas in the prostate gland. In populations with low frequency of HGPIN and high incidence of prostatic carcinoma, perhaps more biopsy cores should be obtained in order to minimize false negative results for premalignant lesions or early adenocarcinoma.

Key words. Prostatic intraepithelial neoplasia. Needle prostate biopsy. Prostatic carcinoma. Mexico.

Frecuencia de la neoplasia intraepitelial prostática de alto grado en la población mexicana

RESUMEN

Introducción. *La neoplasia intraepitelial prostática de alto grado (NIPAG), se considera la única lesión precursora del carcinoma prostático, sin embargo su frecuencia es desconocida en muchos países. Aquí estudiamos la frecuencia de NIPAG en una población donde el carcinoma prostático es común.* ***Material y métodos.*** *Un total de 486 biopsias realizadas de enero del 2001 a enero del 2006 fueron revisadas. Se incluyeron 280 pacientes de clase media o alta de población urbana, de dos hospitales de la Ciudad de México. Con fines comparativos, 206 biopsias de pacientes del Hospital Regional de Tabasco localizado en la zona tropical del país fueron incluidas. Este hospital atiende pacientes de población rural que en general tiene un bajo status socioeconómico.* ***Resultados.*** *De los 486 casos, 162 (33.3%) correspondieron a carcinomas y 319 (65.6%) a condiciones benignas. Sólo en cinco biopsias (1.03%) se observó NIPAG. Tres de los cinco se encontraron en Hospitales de la Ciudad de México y dos en pacientes del Hospital Regional de Tabasco.* ***Conclusiones.*** *Aun cuando estos resultados se obtuvieron sólo en tres centros hospitalarios, ellos sugieren que una baja frecuencia de NIPAG no necesariamente se asocia con una baja frecuencia de carcinoma prostático. La explicación a esta disparidad puede estar relacionada con áreas limitadas de NIP en la próstata. En poblaciones con baja frecuencia de NIPAG y alta incidencia de carcinoma prostático un mayor número de biopsias podría ser necesario para evitar resultados falsos negativos en lesiones preneoplásicas o carcinomas tempranos de la próstata.*

Palabras clave. *Neoplasia intraepitelial prostática. Biopsia por punción. Carcinoma prostático. México.*

INTRODUCTION

High-grade intraepithelial neoplasia (HGPIN) has been recognized as the most likely precursor of invasive carcinoma of the prostate.[1,2] Evidence supporting this relationship includes the spatial association of PIN to carcinoma, the higher frequency of HGPIN in patients with carcinoma, and the phenotypic and genotypic features shared by these two conditions.[2]

The finding of HGPIN on needle biopsies is variable according to several studies, and ranges from 0.7% to 24% of the cases. According to Epstein, the median incidence of HGPIN on biopsy is approximately 5 to 6%.[3] Bostwick, *et al.*, have found that HGPIN is a frequent finding in needle biopsies and is present in up to 16.5% of the cases.[1] The frequency of carcinoma in subsequent biopsies after a diagnosis of HGPIN varies from 10 to 79% when the new biopsy procedure is carried out immediately or after a few years.[2,3] The largest studies reveal carcinoma in 23 to 35% of biopsies with HGPIN.[3-5]

There are several possible reasons for the observed variation in the incidence of HGPIN. The most likely is interobserver variability in making the distinction between low- and high-grade PIN.[3] Others factors that may account for variability in this results include: the limited sample size a needle biopsy represents; the number and quality of histological sections including the concentration of hematoxylin in the standard hematoxylin-eosin stain which, when excessive, can obscure nucleoli; the ethnic group studied, and the source of data, i.e. review of slides or the results registered in clinical files.

The frequency of HGPIN in Mexican population is unknown, and even though comparative studies between Hispanics living in the United States of America (USA) and Caucasians, suggest the absence of differences in the histological findings of prostatic carcinoma among these groups, there is still controversy on this subject.[6]

The purpose of this study was to analyze the frequency of HGPIN in needle biopsies from Mexican patients living in Mexico. According to the Mexican Registry of Malignant Neoplasms and the Mexican Public Health Institute, prostate carcinoma occupies the third place among malignancies in males, after skin and lung cancer.[7]

MATERIAL AND METHODS

A total of 486 cases of 18-gauge prostate needle biopsy specimens performed between January 2001 and January 2006 at any of the three hospitals included in the study were retrospectively reviewed. Two hundred of them were from to the Instituto Nacional de Ciencias Médicas y de la Nutrición, Salvador Zubirán, located in Mexico City. Patients attending this hospital have a medium or high socioeconomic status. Eighty biopsies were from "La Raza" Hospital, also located in Mexico City that receives patients of medium socioeconomic status. For comparison with patients with different socioeconomic status and ethnicity, another 206 biopsies of patients from the Regional Hospital in Tabasco were also included. The latter hospital is located in a tropical zone of the country and receives mostly Indian rural population with low income and low socioeconomic status. This group was included since there have been significant variations in the literature regard the frequency of HGNIP in different races or ethnic groups, even when they belong to the same country.

In HGPIN cases, age of the patient, relevant clinical information, serum levels of prostatic specific antigen (PSA), evolution of the disease and additional biopsies performed, were registered.

Sextant biopsies were performed in all cases and the sextant biopsy protocol was modified when appropriate to obtain from eight to ten needle cores. The samples were fixed in formalin at 10%. The histological slide review was performed on conventional hematoxylin-eosin slides. Three sections of tissue were present on average on each slide. The histological sections varied from 24 to 32, although we did additional ones when areas suspicious of HGPIN or atypical glands were found. In some biopsies we analyzed more than 40 histological sections.

Three pathologists participated in the study, each one with more than 15 years of experience on prostatic pathology. Before analyzing the slides, the three pathologists met for review and consensus on the HGPIN criteria accepted in the literature[1-3] (Figure 1).

Each pathologist reviewed the biopsies of his Institution in order to notice the presence of HGPIN. All cases with NIP were reviewed by the three pathologists in order to achieve a consensus. In cases in which there was disagreement on the PIN grade (high or low grade), the case was classified according to the concordant opinion of two of the three observers. Immunohistochemical studies, using high-molecular weight cytokeratin (HMWCK, clone 34BE12, Dakocytomation, 1:50 dilution) and cytokeratin 5/6 (CK5/6, Dakocytomation, 1:150 dilution), were performed in all cases in which HGPIN was found to corroborate the presence of basal cells.

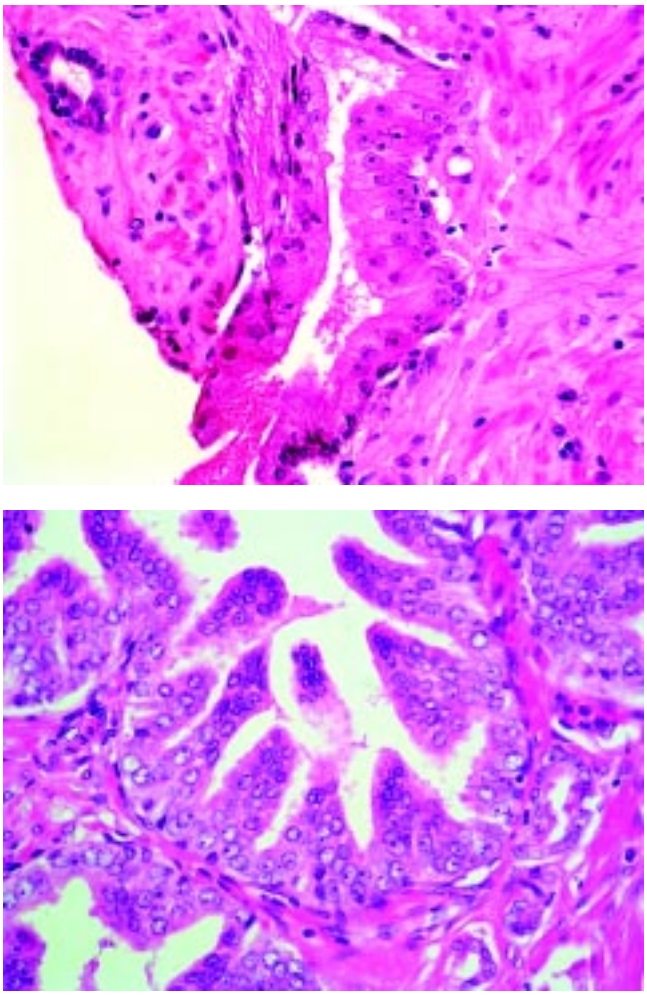

Figure1. High-grade prostatic intraepithelial neoplasia. Prominent nucleoli are seen in the majority of the intraductal cells.

Table 1. Frequency of high grade intraepithelial neoplasia in 486 prostatic biopsies of Mexican patients.

		%
Benign conditions	319	65.64
Prostatic carcinoma	162	33.33
HGPIN	5	1.03
Total	486	100

RESULTS

Results are summarized in table 1. The diagnosis was carcinoma in 162 (33.3%) biopsies and benign conditions in 319 (65.64%). HGPIN was found in 5 biopsies (1.03%). There was disagreement in the diagnosis of HGPIN in two cases. One of them was finally classified as high grade by two pathologists, while the other was classified as low grade and excluded.

Three biopsies with HGPIN were from the hospitals in Mexico City, and two from the Regional Hospital of Tabasco. The age of the patients with HGPIN ranged from 58 to 71 years. Digital rectal examination had been suggestive of malignancy in two of them. PSA serum levels ranged from 7.8 to 23.4 ng./mL. The predominant histological pattern was tufting, found in four of the patients. The remaining case had a papillary pattern. One of the cases showed atypical glands adjacent to the HGNIP, suggestive of early invasion (PINATYP).

Two patients had been lost to follow up after the initial biopsy and no subsequent biopsies were available. In one HGPIN patient, no prostate carcinoma was detected in a subsequent biopsy even when ten cores with additional levels were analyzed, however the PSA levels remained persistently elevated. In the remaining two cases, a subsequent prostate biopsy showed moderately differentiated adenocarcinoma, Gleason score 3 + 3 = 6. In these two patients radical prostatectomy was performed and in both cases the tumor was confined to the prostate gland. HGPIN areas were seen only in occasional histological fields mainly associated with areas of infiltrating prostatic carcinoma. Surgical margins were tumor free, and there were not lymph node metastasis.

DISCUSSION

Considering that HGPIN is the only lesion regarded as precursor of prostatic carcinoma, it is surprising to find that its frequency is unknown in many countries. Worldwide, there is little information available on this subject with the exception of several reports from North America, some European countries, and a limited number of other populations.[8-24] The scant literature on the frequency of HGPIN has been noted previously.[8]

Ethnicity has been regarded by some authors as an important factor for the incidence of HGPIN in prostatic carcinoma. Most of the comparative studies on this subject have been performed in the USA, and have demonstrated that African-American individuals with clinically localized prostate cancer tend to have a more advanced pathological stage at the time of radical prostatectomy compared to Caucasian men, and a higher prevalence of high-grade prostatic intraepitelial neoplasia.[9-12] However, other authors have found that race is not a predictor of prostate cancer in men undergoing repeat prostate biopsies. Accordingly, Carver *et al.*[13] found that

with exception of HGPIN, all other clinical parameters in their study were similar between black and white men.

As mention, in the literature, there is significant variation in the reported frequency of HGPIN, particularly in needle biopsy specimens but also in whole prostatic glands. The frequency of HGPIN in whole prostatic glands ranges form three to 86% in prostates without carcinoma, and from 31 to 100% in prostatectomy specimens with prostatic carcinoma.[14] The factors accountable for these discrepancies include the population studied, the limited sample size that needle biopsies represent diagnostic inconsistencies and, possibly, tissue preparation / staining variables.[15]

However the low frequency of HGPIN in our study does not appear to be related to the number and quality of histological sections since the evaluation was performed on several tissue fragments and the tissue preparation in most cases was of good quality. In addition, the number of tissue fragments obtained in each biopsy and the number of preparations analyzed was similar to those performed in many other studies.[4,5,12-19,23-25]

Even though biopsies in the present study were practiced under clinical and biochemical suspicion of carcinoma and that histological review was thorough, HGPIN was found in only 1.03% of biopsies. This figure is slightly above the 0.7% frequency found in the prostate cancer screening program in the Netherlands by Hoedemaeker *et al*.,[16] and lower than all reported series in community hospitals including some in which the frequency of HGPIN is very low.[17-18]

Our results are consistent with the subjective notion expressed by many pathologist and urologist in Mexico, of HGPIN being a rather unusual finding in needle biopsies. Although the reason for our apparently paradoxical results is still unidentified and remains to be clarified, it is reasonable to speculate that areas of HGPIN in the prostate in our population may not have the same extent or distribution seen in other ethnic groups with a higher frequency of HGPIN. Recently, we have studied 25 radical prostatectomy specimens with carcinoma. Areas of HGNIP were limited to scant histological fields and they were almost always associated with areas that showed prostatic carcinoma. Although these are preliminary data and require further investigation, they suggest that HGPIN is not a diffuse change in the prostatic glands in Mexican men.

An issue that could be related to a low frequency of HGPIN in our country is the genetic background of our population. Mexican men are mostly mestizos (Spanish and Mexican Indian mixture), with a minor group of pure Mexican Indian citizens. This fact it could be important since Mexican Indian population has a close phenotypic and genotypic similitude with Asian population in which the frequency of HGPIN is very low. Cook *et al*.,[19] suggest that, irrespective of birthplace or age, Asian-American men retain one or more genetic or lifestyle characteristics that make their risk of prostate cancer less than that of white residents of the United States. In any case, the frequency of HGPIN here found is also slight than those found in other non-Caucasian populations.[20-22] In contrast, frequency of HGPIN in Spain is clearly higher. A study from Barcelona has revealed a prevalence of HGPIN of 4.4% and an incidence of prostate cancer of 28.7% in cases in which isolated HGPIN was identified at the first biopsy.[23] The incidence of HGPIN in another study was 8%.[24] Even though, prevalence in Spain is still moderately lower than in American Caucasians and significantly lower than in African-Americans.[25] In any case, it must be emphasized that this study only includes three Mexican hospitals and is not necessarily representative of all Mexican population. Additional studies are still necessary in order to know the frequency of HGNIP in our country.

An alternative for low frequency HGPIN populations with a high incidence of prostate carcinoma might be obtaining a greater number of needle cores or even performing a saturation needle biopsy technique, as has been proposed in the diagnosis of HGPIN and prostatic carcinoma.[26-30]

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