

LATENT PROSTATE CARCINOMA IN SINGAPORE CHINESE

By Y. S. Lee and K. Shanmugaratnam

SYNOPSIS

One hundred and fifty six prostates were collected at necropsy from Chinese men over the age of 30 years without clinical evidence of prostatic disease and examined step-serially for malignancy. Latent carcinomas were encountered in 13 (8.3%) cases, whose ages ranged from 42 to 87 years. This figure is high considering the low incidence of overt prostate carcinoma in Singapore (2.7/100,000 males per annum). The lesions were generally small and situated at the periphery subcapsularly. In contrast to overt carcinomas, the majority of latent carcinomas were well differentiated adenocarcinomas of the acinar type. The relationship between latent and overt carcinomas is discussed. The ratio of overt to latent carcinoma increased with age; this ratio was observed to be of a smaller magnitude in Singapore than in areas with high incidence of overt carcinomas. It is suggested that the factors responsible for the promotion of latent to overt carcinoma may be deficient in areas with low incidence of overt carcinoma.

INTRODUCTION

The incidence of clinical or overt prostate carcinoma varies greatly in different parts of the world. The recorded incidence per 100,000 males, standardized to world population, is 65.3 among the negroes in California, 40.0 in New Zealand, 39.0 in Saskatchewan, 33.5 in Sweden, 28.8 in Jamaica, 17.4 in Finland, 12.5 in Israel, 6.5 in India and 3.2 in Japan (Doll *et al*, 1970).

Prostate carcinoma is uncommon in Singapore (Muir, 1962), and is rare among the Chinese (Hu and Chin, 1936). Among the Chinese in Singapore, only 22 cases were recorded by the Singapore Cancer Registry in two years (1968-1969), giving a crude incidence of 1.4 per 100,000 males and an age-standardized incidence (world population) of 2.7 per 100,000 males per annum.

Moore (1935) and Rich (1935) drew attention to the frequent occurrence in autopsy material of latent prostate carcinomas i.e., carcinomas of the prostate that are not clinically manifest; this finding has been consistently confirmed by other workers. It has been uniformly observed that such latent carcinomas occur far more frequently than the overt carcinomas. The nature of latent prostate carcinoma is debatable. A comparison of the frequency of latent carcinomas in areas of high and low incidence may therefore provide useful information. However, while several reports on latent carcinoma have appeared from countries of

high incidence, there have been very few reports from areas of low incidence. Singapore being one of the lowest incidence areas, would therefore be an ideal place to study this problem.

MATERIAL AND METHOD

One hundred and fifty six prostates were randomly collected at necropsy from Chinese males over the age of 30 years who had no clinical evidence of prostatic disease. The causes of death in these cases are shown in Table I. The whole prostate with its capsule was removed with the urinary bladder and surrounding tissues. The dimensions and weight of the prostate were measured after it had been freed from bladder and surrounding tissues. The prostate was then fixed in 10% formalin for at least 10 days, after which the whole organ was cut perpendicular to the urethra into blocks about 4 mm. in thickness. In the majority of cases 5 to 7 blocks were obtained from each gland. Each block was embedded in paraffin and sections cut at a thickness of 5 μ and stained with haematoxylin and eosin.

TABLE I
CAUSE OF DEATH

Causes of Death	All Cases	Latent Ca.
Unnatural Deaths	69	7
Cardiovascular Diseases	32	2
Malignant Neoplasms	18	1
Respiratory Diseases	14	1
Others	23	1
TOTAL	156	13

Department of Pathology, University of Singapore.

Y. S. LEE, M.B., B.S., Lecturer.

K. SHANMUGARATNAM, M.D., Ph.D., F.R.C. Path.,
Professor of Pathology.

Twenty four consecutive cases of adenocarcinoma of the prostate in Chinese males obtained from the biopsy files of the Singapore Institute of Pathology were also reviewed in order to determine whether there were any differences in (a) the histological types and (b) the degree of cellular anaplasia between the latent and overt carcinomas. These were prostatectomy specimens or biopsy (transurethral or needle) specimens obtained from patients with complaints of prostatic disease.

Criteria of Diagnosis

Latent carcinoma of the prostate gland is defined in this study as a lesion which has the histological features of prostatic carcinoma but without any clinical evidence of disease. The criteria of diagnosis were essentially the same as those of overt carcinoma i.e. cellular anaplasia, architectural alterations and invasion.

RESULTS

Frequency

Latent carcinoma was found in 13 (8.3%) of 156 prostates examined from Chinese men over the age of 30 years. This figure was unexpectedly high considering the low incidence of overt prostate carcinoma in Singapore. It is however, relatively low compared to the results of other investigators (Table II).

TABLE II

PERCENTAGE FREQUENCY OF LATENT PROSTATE CARCINOMA IN MALES OVER 50 YEARS (ADJUSTED TO AGE DISTRIBUTION OF SINGAPORE CASES)

Country	% Frequency of Latent Ca.	Author
Canada	16.7	Edward <i>et al</i> (1953)
U.S.A.	30.2	Akazaki <i>et al</i> (1970)
Jamaica	48.0	Baron <i>et</i> Angrist (1941)
England	33.6	Franks (1954)
Austria	19.7	Moore (1935)
Japan	17.2	Oota (1961)
Singapore	10.8	Present Series

Age Distribution

No case of latent prostatic carcinoma was encountered in the 4th decade. The cases ranged from 42 to 87 years of age. The frequency of latent carcinoma showed a progressive rise in the older age groups (Table III).

Multiplicity of Foci

Two foci of carcinoma, well separated from each other, were seen in 3 cases. There was therefore a total of 16 foci of latent carcinoma in the 13 prostates.

Size

Majority of the latent carcinomas were very small. Eight foci were less than 5 mm. in maximum dimension, and only 2 foci exceeded 1 cm.

Location

Thirteen of the sixteen carcinomatous foci were situated at the periphery subcapsularly. No carcinoma was found in the median lobe or the inner glands where nodular hyperplasia develops. All quadrants of the gland were equally involved (Fig. 1).

Invasion

Invasion of the stroma was seen in all cases. Direct invasion of the cancer into the lumen of vessels was not observed, but nine cases showed malignant acini in close proximity to thin-walled vessels (Fig. 2) or infiltration of the fibrous tissue surrounding larger vessels. Infiltration of the perineural spaces (Fig. 3) and sometimes of the nerve itself were observed in 8 cases. Capsules were invaded in 4 cases (Fig. 4) and only in 1 case was the urethra involved (Fig. 5, Table IV). Routine histological examinations of the regional lymph-nodes were not done but no obvious metastases were noted at necropsy.

Histological Appearance of Latent Carcinomas

All the latent carcinomas were adenocarcinomas. No squamous cell, transitional cell or anaplastic carcinomas were encountered. Based on the histological appearances, the lesions were classified into acinar, tubular, cribriform and poorly differentiated adenocarcinomas.

ACINAR CARCINOMA

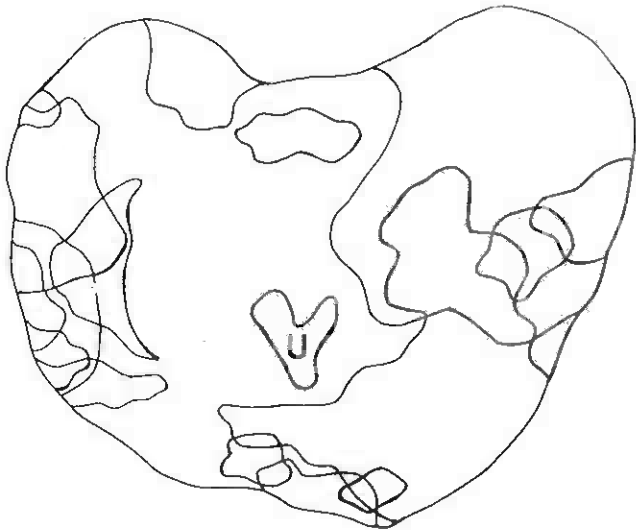
These were characterised by well differentiated pale-staining oval or round acini with a tendency to form cohesive aggregates; there was little cellular anaplasia (Fig. 6).

TUBULAR CARCINOMA

These were characterised by dark-staining tubular or branching glands often showing cellular anaplasia; there was little tendency to form cohesive aggregates (Fig. 7).

CRIBRIFORM CARCINOMA

These were characterised by intraluminal proliferation of the malignant epithelium or aggregation of many acini with common septae, giving rise to a sieve-like appearance (Fig. 8).



DISTRIBUTION OF 16 FOCI OF
LATENT PROSTATE CARCINOMA

Fig. 1. Distribution of 16 foci of latent prostate carcinoma.



Fig. 4. Shows an infiltrative carcinoma with invasion of the capsule of the prostate gland (H & E \times 75).

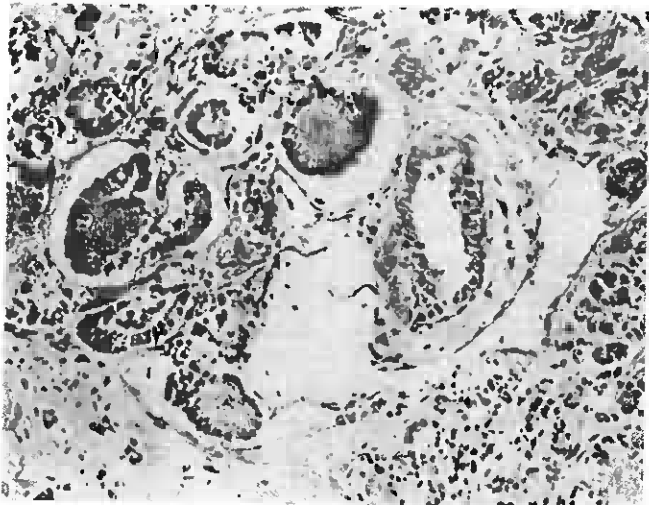


Fig. 2. Shows malignant acini in close proximity to thin-walled vessels (H & E \times 150).

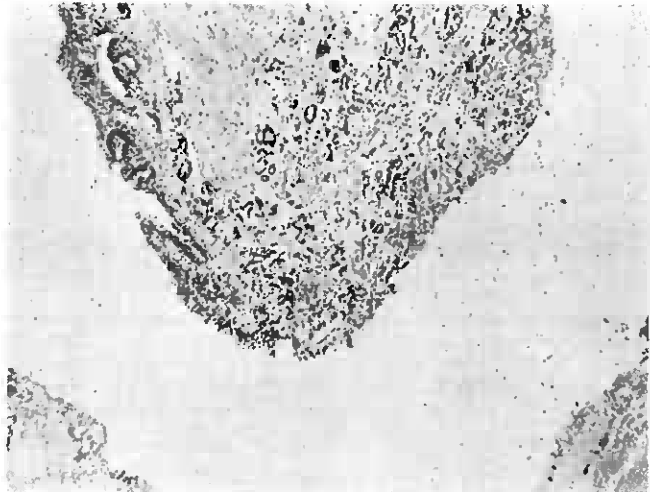


Fig. 5. Shows infiltration of the urethra by small hyperchromatic tumour acini (H & E \times 45).



Fig. 3. Shows a tubular carcinoma with infiltration of the perineural space (H & E \times 75).

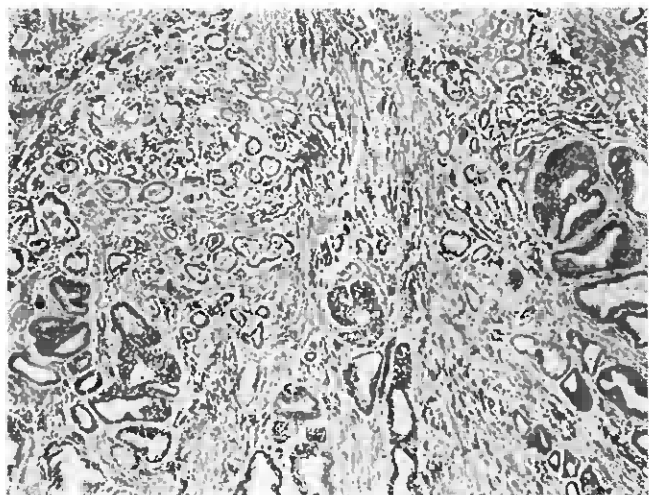


Fig. 6. Acinar carcinoma. Tumour composed of well differentiated pale-staining oval or round acini with a tendency to form cohesive aggregates. There is little cellular anaplasia (H & E \times 45).

TABLE III
AGE DISTRIBUTION

Age Group	No. Cases	No. Ca.	%
30-39	22	0	0.0
40-49	23	1	4.3
50-59	36	3	8.3
60-69	47	5	10.6
70-79	23	3	13.0
80+	5	1	20.0
TOTAL	156	13	8.3

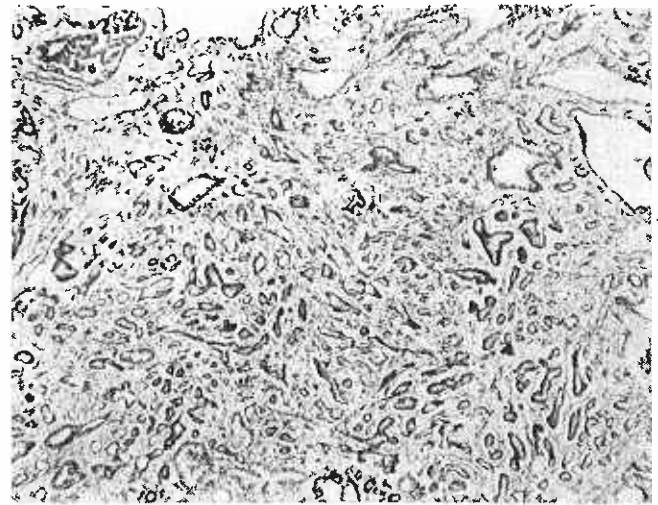


Fig. 7. Tubular carcinoma. Tumour composed of dark-staining tubular or branching glands with cellular anaplasia and little tendency to form cohesive aggregates (H & E \times 45).

TABLE IV
INVASION OF LATENT PROSTATE
CARCINOMA

Structures Involved	Cases (13)	Foci (16)
Capsule	4	4
Nerve	8	9
Vessel	9	11
Urethra	1	1

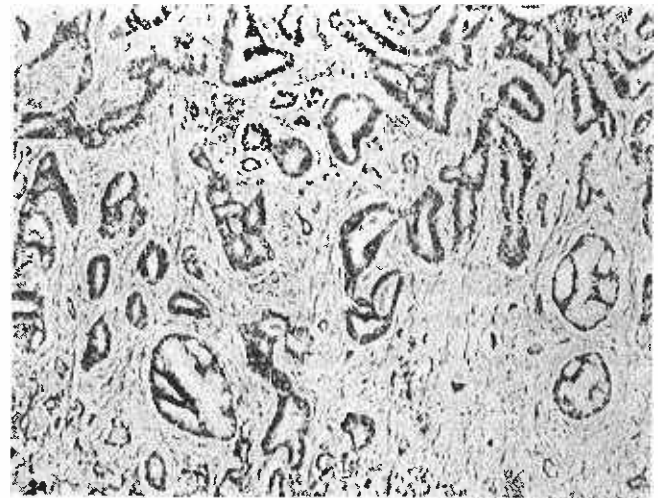


Fig. 8. Cribriform carcinoma. Shows intraluminal proliferation of the epithelium and aggregation of many acini with common septae, giving rise to a sieve-like appearance (H & E \times 75).

TABLE V
COMPARISON OF THE RATIO OF THE
INCIDENCE OF OVERT CARCINOMA TO
THE PREVALENCE OF LATENT CARCI-
NOMA IN HIGH AND LOW INCIDENCE
AREAS

Age Group	U.S.A.* Baron <i>et</i> Angrist	England* Franks	Denmark* Starklint	Singapore Present Series
40 - 49	—	—	—	1:5375
50 - 59	1:1909	1:1318	1:962	1:2128
60 - 69	1:304	1:320	1:248	1:797
70 - 79	1:167	1:101	1:139	1:422†
80+	1:153	1:101	1:166	—

*Quoted from Higginson and Simson (1961)

†Age 70+

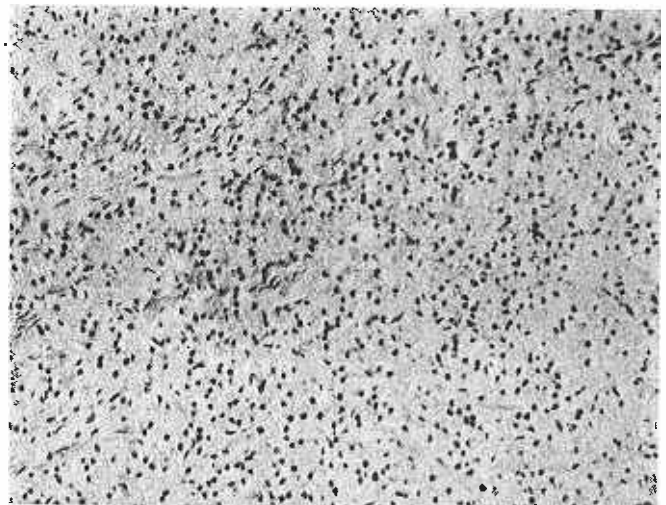


Fig. 9. Poorly differentiated adenocarcinoma. Tumour composed of a sheet of cells without good glandular differentiation (H & E \times 150).

POORLY DIFFERENTIATED ADENOCARCINOMA

These were tumours in which glandular structures were not well formed (Fig. 9).

On the basis of this classification, there were 9 foci of acinar carcinoma, 4 tubular, 1 cribriform and 2 poorly differentiated adenocarcinomas.

The acinar carcinomas differed from the other histological types in that they were smaller, less infiltrative, less anaplastic and tended to occur in the younger age-groups.

Histological Appearance of Overt Carcinomas

All the 24 cases were adenocarcinomas. Only one of these was an acinar carcinoma. There were 7 tubular carcinomas, 2 cribriform carcinomas and 11 poorly differentiated carcinomas; 3 cases were unclassified on account of the small size of the specimens.

Cellular anaplasia was a constant feature. Mitoses, which were rare in latent carcinomas, were seen in as many as two thirds of cases. The tumours were generally large and extensively infiltrative.

Ratio of Overt to Latent Carcinoma

The ratio of the incidence of overt carcinoma to the percentage frequency of latent carcinoma increased with age. This ratio was observed to be of a smaller magnitude in Singapore, in all age groups that were compared, than in areas with high incidence of overt carcinoma.

DISCUSSION

The nature of latent prostatic carcinomas is problematic. These lesions have the histological and the locally infiltrative characteristics of malignancy but lack the capacity for rapid growth. On the basis of age-specific incidence, Ashley (1965) considered that overt and latent carcinomas were not biologically identical. On the other hand McNeal (1969), using volume distribution data concluded that both overt and latent prostatic carcinoma belonged to a single group in which the growth rate at any time was a logarithmic function of tumour size.

The present study suggests that cellular anaplastic change might be an important factor in the progression from latent to overt carcinomas. Cellular anaplasia was a constant and marked feature in overt carcinomas. It was also evident in the larger and more aggressive latent carcinomas but not in the small acinar type. The factors responsible for this anaplastic transformation are not known. In these factors may lie the explanation for the big difference between the prevalence of latent and overt prostate carcinomas.

The majority of the latent carcinomas in Singapore were of the acinar type which showed little cellular anaplasia and limited infiltration. Akazaki *et al* (1970) also noted that the frequency of "proliferative type" of latent carcinoma was significantly higher in the United States and Columbia than in Japan, and that there was a remarkable difference between the morphology of latent carcinoma in native Japanese and in Japanese migrants in Hawaii, the latter resembling closely that in Continental Americans in U.S.A. and Columbia. There is therefore evidence to suggest that latent carcinomas of the prostate are not homogeneous lesions but comprise of histological types that differ in histological appearances, cellular anaplasia and infiltrative aggressiveness. An attempt to classify them into "active or aggressive" lesions and "inactive or dormant" lesions based on these differences appears to be justified.

Although overt prostatic carcinoma is exceptionally rare in Singapore, latent carcinomas are by no means uncommon. Latent carcinomas, however, appeared to occur less frequently in Singapore than in countries with a high incidence of overt carcinoma. Some of these differences may well be due to observer variation and possible differences in diagnostic criteria. A joint study in areas with high and low incidence of overt prostate carcinoma, using uniform criteria of diagnosis may therefore provide more reliable information.

The differences between the incidence of overt carcinoma in Singapore and in countries with high incidence was more marked than the differences in the frequency of latent carcinoma. Furthermore, the ratio of overt to latent carcinoma was of a smaller magnitude in Singapore than in areas with high incidence of overt carcinoma. It appears, therefore, that the latent prostatic carcinomas in Singapore have a lesser tendency to become overt. It is suggested that the factors (genetic, hormonal or environmental) that are responsible for the promotion of latent to overt carcinoma may be deficient in Singapore.

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