

# Time Trends in Histological Features of Latent Prostate Cancer in Japan

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**Purpose:** The incidence of prostate cancer is reported to be increasing in Asia, including Japan. Although this trend has been attributed partly to a more Western diet, this assumption may involve variable confounders. Thus, we examined the histological features of contemporary vs historical latent prostate cancer.

**Materials and Methods:** Prostate specimens from a consecutive autopsy series (127, present study, 2008 to 2013) were examined. Each prostate gland was fixed and sliced in step sections. The findings were compared to those from another autopsy series (501 subjects, 1983 to 1987) at our institution.

**Results:** The mean age of subjects in the present study was 68.9 years while the mean age was not available from the earlier study. However, the mean age of the 566 entrants in the expanded database (1983 to 1989) was 63.5 years ( $p=0.0001$ ). Prostate weight was significantly greater in the present study ( $p < 0.0001$ ). Latent prostate cancer was found more frequently in the present study than in the previous study (43.3% and 20.8%, respectively,  $p < 0.0001$ ). No distinct difference was seen in the proportion of tumor grade between the groups. An increasing trend of moderately to poorly differentiated tumors with advancing age was more evident in the present study. Index cancer volume was greater in the present study with 25.5% measuring 500 mm<sup>3</sup> or greater vs only 9.6% of cancers in the previous study ( $p=0.008$ ).

**Conclusions:** Chronological changes in the histological characteristics of Japanese latent prostate cancer were noted as it is more prevalent in the contemporary series. Our data may reflect a worldwide trend in increasingly aging societies.

**Key Words:** prostatic neoplasms, histology, age factors

REMARKABLE racial and ethnic differences in the incidence of prostate cancer have been reported, ranging from 4.4 per 100,000 in India to 118.2 per 100,000 in the U.S.<sup>1</sup> However, the incidence of PCa has been increasing worldwide in recent years, even in Asian countries.<sup>2</sup> This trend is

especially noticeable in northeast Asia, including Japan, where the incidence of PCa had previously been relatively low.<sup>1,2</sup> The cause of this trend is complicated and may be multifactorial, with a possible explanation being the rapid increase in the Japanese elderly population.<sup>3</sup>

## Abbreviations and Acronyms

BPH = benign prostatic hyperplasia  
GS = Gleason score  
HE = hematoxylin and eosin  
PCa = prostate cancer  
PSA = prostate specific antigen

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Another possible reason for this trend is changes in lifestyle due to a more Western diet.<sup>4,5</sup> During the last 30 years Japanese dietary habits have shifted toward the consumption of meat and poultry and away from fish and shellfish, which means increased intake of animal fat.<sup>6</sup> At the same time obesity has become more commonplace, now affecting around 30% of Japanese males.<sup>7,8</sup> Epidemiological studies of Japanese immigrants to the U.S. have shown a much higher incidence of PCa compared with their contemporaries in Japan and those findings may now apply to Japanese men who reside in Japan but follow a more Western lifestyle.<sup>9</sup>

The rate of PCa might also be statistically biased due to the spread of early detection strategies such as PSA screening and the accuracy of cancer registration systems.<sup>10</sup> For example, PSA screening is becoming more common in Japan, although it is still only performed in 40% among men older than 50 years vs 80% or more in the U.S.<sup>10,11</sup> In addition, an accurate determination of PCa incidence requires a mature national reporting system, which is not yet available in many Asian countries.

Although variability in cancer registration systems and in the availability of PSA screening in each country can introduce significant bias in PCa incidence, we believe that observations of latent PCa in autopsy should give less biased information and provide insight despite these confounders.

Yatani et al compared the frequency of latent PCa in Japanese autopsy cases from 1965 to 1979 with that of cases from 1982 to 1986.<sup>12</sup> The prevalence of PCa increased from 22.5% to 34.6% between the 2 periods and the number of pathologically aggressive tumor phenotypes also increased. Because of lifestyle changes and the increased proportion of the aged population in recent decades, we investigated changes with time, comparing the prevalence and characteristics of latent PCa in the contemporary Japanese population with a prior characterization of PCa prevalence and characteristics reported from the same institution more than 20 years ago.<sup>13</sup>

## MATERIALS AND METHODS

Prostate specimens from a consecutive autopsy series of men age 20 or older (127, present study) at Jikei University Hospitals were procured between 2008 and 2013. None of the subjects had a history of treatment for prostatic diseases including PCa. Findings were compared with an autopsy series (501) conducted from 1983 to 1987 by Wada et al at the same institution.<sup>13</sup>

Prostate glands were procured within 24 hours after death. Each gland together with seminal vesicles was weighed and fixed in 10% formalin, and subsequently sliced in step sections vertical to the urethra at 3 mm intervals in the study by Wada et al<sup>13</sup> and 4 mm intervals

in the present study. Each section was paraffin embedded, and slides were prepared from 5  $\mu$ m sections that were stained with hematoxylin and eosin. A single pathologist (MF in the earlier study and HT in the present study) diagnosed latent PCa based solely on HE findings. Tumor grade was assigned according to the Gleason grading system in the present study and the 1980 WHO histological classification in the study by Wada et al.<sup>14</sup> Comparisons of tumor grade between the groups were conducted using the 1980 WHO grading system due to the unavailability of HE slides for review from the earlier study. In the 1980 WHO histological classification, tumor grade was stratified into well, moderately and poorly differentiated adenocarcinoma based on the architectural features. Cancer volume in the present study was estimated by using previously described methods.<sup>13</sup> Microscopy images of cancer lesions were acquired under the same magnification and cancer lesion area was measured with a digitizer (Cosmozone III, Nikon Corp, Tokyo, Japan). Lesion volume was calculated by multiplying by the thickness of 4 mm. The total volume of each cancer was determined by integrating the value of each slice and adjusting by a conversion factor of 1.33. The predominant lesion from each case was deemed the representative cancer for that case (index cancer) and used for comparison. Cancer volume in the study by Wada et al was referenced from the original report.<sup>13</sup> The approach to estimating cancer volume was identical to the present study except for slice thickness (3 mm).

We referred to the autopsy database of Wada et al (581 subjects, 1983 to 1989), which had been expanded after study completion, to enable the statistical analysis of individual data with information that was not available in the original study. Thus, comparison of age and prostate weight was conducted for 566 subjects 20 years old or older (Wada et al expanded cohort).

Statistical analysis using the Student t-test and chi-square test was performed with GraphPad Prism® 5. Age adjusted logistic regression analysis was conducted using SAS® v.9.2. Levels of statistical significance were set at  $p < 0.05$ .

## RESULTS

### Comparison of Prostate Weight

In the present study we examined 127 specimens and compared the results to those obtained from the study by Wada et al.<sup>13</sup> Mean age in the present study was 68.9 years (range 24 to 92) vs 63.5 years (range 0 to 102) for the 566 men 20 years old or older in the expanded cohort. The difference in mean age between the groups was significant ( $p = 0.0001$ ), which most likely reflects recent life expectancy increases in Japan. Prostate weight was significantly greater in the present study than in the expanded cohort (22.8 vs 33.1 gm,  $p < 0.0001$ ). Cross-sectional findings of prostate weight may mirror the natural course of prostate growth. In the expanded cohort prostates grew during the subjects' 20s, plateaued during the 30s and then began to

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