Comparison of Prostate-Specific Antigen and Hormone Levels among Men in Singapore and the United States

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Abstract

Prostate cancer incidence rates markedly vary between countries. The highest rates of prostate cancer are observed in Western countries such as the United States, whereas the lowest rates are seen in Asian countries such as Singapore. To gain an understanding of the difference in prostate cancer burden between low-risk and high-risk populations, we examined serum prostate-specific antigen (PSA) levels among Singapore-Chinese men (n = 315) from the Singapore Chinese Health Study and African-American (n = 440), U.S. White (n = 355), U.S. Latino (n = 523), and Japanese-American (n = 349) men from the Hawaii-Los Angeles Multiethnic Cohort Study. All men had no history of prostate cancer at the time of blood draw. PSA measurements were assayed by one centralized diagnostic facility. Testosterone and 3α-androstanediol glucuronide levels were evaluated in a subsample of men. Scheffe’s multiple comparison tests were used to evaluate differences in PSA and hormone levels between groups. PSA levels among the Singapore-Chinese (geometric mean = 1.43 ng/mL) were similar to that of African-Americans (1.46 ng/mL), U.S. Whites (1.28 ng/mL), and Japanese-Americans (1.22 ng/mL) and significantly higher than U.S. Latinos (1.18 ng/mL; P = 0.038). Although there was a strong correlation (R² = 0.89) between PSA levels and U.S. ethnic group–specific prostate cancer incidence rates before PSA screening (1983-1987), the levels among the Singapore-Chinese completely failed to relate to their low incidence rate. Testosterone and 3α-androstanediol glucuronide levels did not reflect racial/ethnic patterns of disease. Our results highlight a potentially large group of Singapore-Chinese men with undiagnosed prostate cancer. Given that the overall mortality rate of prostate cancer in Singapore is low, these undiagnosed cancers may be of nonaggressive type. Alternatively, PSA may be a poor marker of prostate cancer in this low-risk population. (Cancer Epidemiol Biomarkers Prev 2005;14(7):1692–6)

Introduction

Prostate cancer is the most commonly diagnosed cancer among men in Western countries, and the disease is marked by dramatic international differences (1). Over the period 1983 to 1987, before the advent of prostate-specific antigen (PSA) screening, the age-standardized incidence rate of prostate cancer in the United States was 82.7 per 100,000 among African-Americans, 62.8 among U.S. Whites, and 7.6 among Singapore-Chinese (2). These rates increased dramatically in the United States with the dissemination of PSA screening in the early 1990s (3), and in Singapore where population PSA testing is not practiced, a 2-fold increase in incidence was nevertheless observed over the 10-year period from 1983 to 1987 and from 1993 to 1997 (2, 4). In 1998, an ~3-fold difference in mortality rates was observed between the United States and Singapore, 14.0 and 5.2 per 100,000, respectively (5).

To further understand the difference in prostate cancer burden between low-risk and high-risk populations, we examined PSA levels, a marker for disease, among males with no history of prostate cancer in the Singapore Chinese Health Study and the Hawaii-Los Angeles Multiethnic Cohort Study (6, 7). In addition, we also investigated whether serum levels of testosterone and 3α-androstanediol glucuronide reflect the racial/ethnic differences in prostate cancer risk. 3α-Androstanediol glucuronide is a metabolite of dihydrotestosterone, the more active form of testosterone in the prostate.

Materials and Methods

Study Population. Study subjects are participants in the Singapore Chinese Health Study and the Hawaii-Los Angeles Multiethnic Cohort Study. Both studies are population-based prospective investigations with an emphasis on environmental and genetic factors related to cancer etiology. This study was approved by the Institutional Review Boards at the National University of Singapore, the University of Hawaii, and the University of Southern California.

Singapore Chinese Health Study. From 1993 to 1998, 63,257 men and women, ages 45 to 74 years, who were residents of government housing estates (86% of the Singapore population resided in such facilities during the study enrollment period), were enrolled in the Singapore Chinese Health Study. At recruitment, each participant was interviewed in person by a trained interviewer using a validated 165-item food frequency questionnaire. The questionnaire also requested demographic information, lifetime use of tobacco, current alcohol drinking pattern, current physical activity profile, reproductive history (women only), occupational exposures, medical history, and family history of cancer. Further study details are described elsewhere (6).

The study reported here included blood samples collected from 1994 to 1998 from a random sample of cohort subjects. A 20-mL blood sample was obtained from each volunteer. Most blood samples were collected in the morning, with no

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The correlation coefficient for samples with repeat PSA measurements (12%) was 0.99. Hormone levels were measured on a sample of subjects with PSA measurements. Serum hormone levels for both cohorts were assayed by the Reproductive Endocrine Research Laboratory at University of Southern California (F. Stanczyk). Total testosterone was assayed by alumina column chromatography and RIA (8). 3α-Androstanediol glucuronide was quantified by direct RIA using an 125I-Androstanediol Glucuronide kit (Diagnostic Systems Laboratories, Inc., Webster, TX) as previously described (9). The mean intraassay and interassay coefficients of variation for testosterone were 5.7% and 2.7%, respectively. For 3α-androstanediol glucuronide, the mean intraassay and interassay coefficients of variation were 5.2% and 3.6%, respectively.

### Incidence and Mortality Data

Age-standardized incidence rates of prostate cancer were abstracted from the IARC Cancer Incidence in Five Continents, volumes III to VIII (2, 4, 10-13). Age-standardized incidence rates from the 5-year period 1983 to 1987 were used to reflect the incidence rate of prostate cancer before the widespread use of PSA screening in the United States. To reflect the major sources of racial/ethnic groups in the Multiethnic Cohort Study, Los Angeles incidence data were used for African-Americans and U.S. Latinos and Hawaii incidence data were used for Japanese-Americans and U.S. Whites.

Age-standardized incidence and mortality rates of prostate cancer in Singapore from 1968 to 1997 were used to evaluate secular trends. Mortality rates from the website databases of WHO and the National Cancer Institute Surveillance, Epidemiology, and End Results program were used (5, 14).

All rates were standardized to the World Standard Population (15).

### Statistical Analysis

To evaluate differences in PSA levels between the groups, we calculated for each group the age-specific geometric mean PSA levels for three 10-year age categories (45-54, 55-64, and 65-74 years). The overall age-standardized geometric mean was calculated for each group by direct standardization methods. The combined age distribution of the Singapore Chinese Health Study and the Multiethnic Cohort Study was used for standardization. Scheffe’s multiple comparison test was used to evaluate the statistical significance of differences in PSA levels (16). To examine the association between PSA levels and prostate cancer incidence rates in populations of the Multiethnic Cohort Study, we fitted a linear regression model between the incidence rates of prostate cancer (1983-1987) for African-Americans, U.S. Whites, U.S. Latinos, and Japanese-Americans and the age-standardized geometric mean PSA levels.

To compare testosterone and 3α-androstanediol glucuronide levels between the five racial/ethnic groups, we used a mixed model analysis incorporating random effect adjustment for assay variability and fixed covariate effect of age. Age was

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**Table 1. Distribution of study subjects and PSA levels by age and ethnic group**

<table>
<thead>
<tr>
<th>Age* (y)</th>
<th>Singapore-Chinese</th>
<th>African-Americans</th>
<th>U.S. Whites</th>
<th>U.S. Latinos</th>
<th>Japanese-Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>PSA (ng/mL)</td>
<td>n</td>
<td>PSA (ng/mL)</td>
<td>n</td>
</tr>
<tr>
<td>45-54</td>
<td>117</td>
<td>0.96 (0.06)</td>
<td>66</td>
<td>0.83 (0.07)</td>
<td>78</td>
</tr>
<tr>
<td>55-64</td>
<td>120</td>
<td>1.41 (0.11)</td>
<td>159</td>
<td>1.24 (0.11)</td>
<td>159</td>
</tr>
<tr>
<td>65-74</td>
<td>78</td>
<td>1.69 (0.19)</td>
<td>215</td>
<td>2.00 (0.14)</td>
<td>118</td>
</tr>
<tr>
<td>Total</td>
<td>315</td>
<td>1.43 (0.09)</td>
<td>440</td>
<td>1.46 (0.07)</td>
<td>355</td>
</tr>
</tbody>
</table>

**NOTE:** Data expressed as geometric mean levels with SEs.

*Mean age (SD) was 58.0 (7.9) in Singapore-Chinese, 63.3 (7.5) in African-Americans, 60.9 (7.0) in U.S. Whites, 62.9 (6.5) in U.S. Latinos, and 61.6 (7.6) in Japanese-Americans.

*Age standardized.

*Compared with Singapore-Chinese, P = 0.038.
used as a continuous variable. Statistical analyses were done on logarithmically transformed values. Scheffe’s multiple comparison correction was also applied.

All significance levels (Scheffe adjusted P values) noted were two sided.

### Results

Table 1 shows the geometric mean PSA levels in Singapore-Chinese and U.S. men. Geometric mean PSA levels increased significantly (P < 0.001) with age for each group as expected. The age-standardized geometric mean PSA level of PSA levels increased significantly (1.43 ng/mL) was slightly less than that of African-Americans (1.46 ng/mL); these values were higher than the geometric mean levels of U.S. Whites, Japanese-Americans, and U.S. Latinos (Table 1). The levels in Singapore-Chinese were statistically significantly higher than those of U.S. Latinos (P = 0.038). African-Americans had significantly higher levels than U.S. Latinos (P = 0.010). Also, African-Americans had higher levels than Japanese-Americans (uncorrected P = 0.008), but this was not statistically significant with Scheffe’s adjustment (P = 0.129). The PSA levels of the Singapore-Chinese were higher at all age groups than that of U.S. Whites, U.S. Latinos, and Japanese-Americans. In comparison with African-Americans, the levels of the Singapore-Chinese were higher for the two age groups, 45 to 54 and 55 to 64 years, and lower for the age group of 65 to 74 years. These last differences were not statistically significant.

Table 2 shows the percentage of subjects having PSA values ≥4 ng/mL by age and ethnic group. African-Americans had the highest proportion of subjects with PSA values ≥4 ng/mL. Among the Singapore-Chinese, the percentage of PSA values ≥4 ng/mL was close to that of African-Americans in each age group. The Singapore-Chinese and U.S. groups displayed similar distributions at levels of PSA <1 to 1.99 ng/mL and 2 to 3.99 ng/mL at all age groups (data not shown).

Among U.S. males from 1983 through 1987, African-Americans had the highest incidence rate of prostate cancer (82.7 per 100,000), followed by U.S. Whites (62.8), with the lowest incidence rates observed in U.S. Latinos (38.4) and Japanese-Americans (34.4). Figure 1 shows that the age-standardized geometric mean PSA values for these ethnic groups in the Multiethnic Cohort Study were highly correlated with the ethnic variation in prostate cancer incidence (R² = 0.89). The figure also shows that the Singapore-Chinese displayed a high geometric mean PSA level despite their low incidence rate of prostate cancer (7.6 per 100,000).

The trends in prostate cancer incidence and mortality in Singapore are shown in Fig. 2. During the 30-year period from 1968 through 1997, the incidence and mortality rates in Singapore increased steadily with a sharp increase in incidence from 1993 to 1997. Overall, a 4-fold increase in prostate cancer incidence was observed from 1968 to 1972 (3.6 per 100,000) and from 1993 to 1997 (14.4). Prostate cancer mortality increased 2.35-fold from 2.3 per 100,000 in 1968 to 1972 to 5.4 per 100,000 in 1993 to 1997.

Table 3 shows the geometric mean levels of total testosterone and 3α-androstanediol glucuronide. No significant differences in geometric mean total testosterone levels were observed between any of the racial/ethnic groups. U.S. Whites had the highest 3α-androstanediol glucuronide levels (5.48 ng/mL); this was statistically significantly greater than the levels of Japanese-Americans (3.59 ng/mL; P < 0.0001) and Singapore-Chinese (4.20 ng/mL; P = 0.007). U.S. Latinos (4.96 ng/mL) also had significantly higher levels of 3α-androstanediol glucuronide compared with Japanese-Americans (P = 0.004).

### Discussion

This study revealed that PSA levels in Singapore-Chinese men were higher than U.S. White, U.S. Latino, and Japanese-American men at all ages. Overall, their levels were comparable to high-risk African-American men, although the levels among the Singapore-Chinese were higher at the ages of 45 to 64 years and lower at the ages of 65 to 74 years. The low incidence rate of prostate cancer in Singapore fails to relate to their levels of PSA. Yet, the incidence and mortality rates in Singapore indicate a growing rise in the disease. Given that population screening of prostate cancer is not recommended in Singapore, it is unlikely that PSA testing in Singapore has had a major influence on prostate cancer rates over the time period we have examined. Our results highlight a potentially large, previously unrecognized group of men in Singapore with substantially elevated PSA levels, indicating...
Table 3. Geometric mean concentrations and 95% confidence intervals of testosterone and 3α-androstanediol glucuronide by ethnic group

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Total Testosterone (ng/mL)</th>
<th>3α-Androstanediol Glucuronide (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (95% confidence interval)</td>
<td>Mean (95% confidence interval)</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td>n</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singapore-Chinese</td>
<td>228</td>
<td>220</td>
</tr>
<tr>
<td></td>
<td>4.90 (4.54-5.29)</td>
<td>4.20 (3.68-4.80)</td>
</tr>
<tr>
<td>African-Americans</td>
<td>129</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>4.36 (4.00-4.76)</td>
<td>4.33 (3.68-5.10)</td>
</tr>
<tr>
<td>U.S. Whites</td>
<td>159</td>
<td>163</td>
</tr>
<tr>
<td></td>
<td>4.73 (4.37-5.12)</td>
<td>5.48 (5.41-5.55)</td>
</tr>
<tr>
<td>U.S. Latinos</td>
<td>130</td>
<td>131</td>
</tr>
<tr>
<td></td>
<td>4.49 (4.12-4.89)</td>
<td>4.96 (4.30-5.72)</td>
</tr>
<tr>
<td>Japanese-Americans</td>
<td>184</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>4.70 (4.35-5.09)</td>
<td>3.59 (3.11-4.15)</td>
</tr>
</tbody>
</table>

NOTE: Testosterone and 3α-androstanediol glucuronide levels adjusted for age at blood draw and assay batch. Mean concentrations presented for hypothetical man of 61.6 years (overall mean age of blood draw).

*p < 0.05.

1Compared with Singapore-Chinese, P < 0.01.

2Compared with Japanese-Americans, P < 0.01.

Previous studies have reported a substantially smaller difference in prostate cancer rates between Japanese-American and native Japanese men compared with the reported incidence rates if similar detection practices were followed (18, 19). Differences in screening practices between Singapore and the United States may have biased our comparison of PSA values. In Singapore, the Ministry of Health does not advocate population screening for prostate cancer (20), whereas in the United States prostate cancer screening by PSA testing has had widespread adoption since 1989. PSA screening enhances lead time in diagnosis and increases the number of prevalent cases in the population (21). In the Multiethnic Cohort Study, ~6% of African-American, 60% of U.S. White, 46% of U.S. Latino, and 48% of Japanese-American men reported having had a PSA test. Our sample excludes all prostate cancer cases, including those diagnosed solely on the basis of PSA findings. Had these PSA-only diagnosed men not undergone PSA screening, they would have been eligible for our sample, and consequently our U.S. values were slightly artificially low.

To bring the Singapore incidence rate of prostate cancer in line with their levels of PSA (based on the U.S. PSA incidence rate association shown in Fig. 1), we would have to exclude the top 20% of PSA values of the Singapore-Chinese. With this mimicking of the effect of PSA screening if it was applied to Singapore, it is unreasonable that such a large percentage of the Singapore-Chinese would be identified as having disease. Thus, differences in screening practices alone cannot explain the comparable PSA levels in Singapore and the United States despite their markedly different risk of disease.

We also examined the correlation between the ethnic group-specific mortality rates of prostate cancer (1998) and the age-standardized geometric mean PSA levels (data not shown). A high correlation ($R^2 = 0.91$) was observed between PSA levels and mortality rates in our U.S. groups, yet PSA levels in the Singapore-Chinese failed to correlate with their low prostate cancer mortality as was similarly seen with incidence. The reported mortality rate of prostate cancer may be influenced by diagnostic practices and accuracy of classification of prostate cancer as the underlying cause of death. How such factors may have influenced the reporting of prostate cancer deaths in Singapore is unclear.

As differences in screening practices cannot entirely explain the variation in prostate cancer rates between the two populations, we propose that some aspect of Western lifestyle may act to potentiate latent disease detected by PSA measurement. We propose that recent incorporation of a Western lifestyle in Singapore may have increased exposure to factors that cause progression of latent disease to clinical prostate cancer and/or may have resulted in a reduction of exposure to factors that traditionally protect Chinese men from clinical disease. Singapore has undergone rapid industrialization over
the past three decades and, coupled with an aging population, a shift towards chronic diseases affected by obesity, reduced physical activity, and other similar lifestyle changes has been observed (22). In a comparison of incidence and mortality rates of prostate cancer from 1973 to 1977 and from 1988 to 1992, among five low-risk populations, Singapore displayed the largest percent change in incidence and mortality, 104.2% and 94.7%, respectively (23).

We also examined ethnic differences in circulating levels of testosterone and 3α-androstenediol glucuronide. No differences in testosterone levels were observed among different racial/ethnic groups in our population of older men. The biologically active form of testosterone is considered to be the fraction of testosterone that is not bound to sex hormone binding globulin. Recent prospective studies have not shown an association with either free or total testosterone levels and prostate cancer risk (24, 25). However, a study by Gann et al. (26) found a significant trend of increasing prostate cancer risk when testosterone levels were adjusted for levels of sex hormone binding globulin. A longitudinal study of young Black and White men (ages 24–31 years at hormone measurement) reported that previous racial differences in testosterone levels may be attributed to racial differences in abdominal obesity (27). 3α-Androstenediol glucuronide levels have been found to be higher in U.S. Whites compared with African-American and Asian populations (28, 29). Findings from this study are consistent with previous reports.

Acknowledgments

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