Serum Levels of Prostate-Specific Antigen Among Japanese-American and Native Japanese Men

Atsuko Shibata, Alice S. Whittemore, Kyoichi Imai, Laurence N. Kolonel, Anna H. Wu, Esther M. John, Thomas A. Stamey, Ralph S. Paffenbarger*

Background: Fourfold to sixfold higher prostate cancer rates in Japanese-American men in the United States compared with Japanese men in Japan have been cited to support a role for environmental risk factors in the etiology of the disease. To examine the hypothesis that part or all of the elevated prostate cancer rates in Japanese-American men may reflect more intensive prostate cancer screening in the United States than in Japan, we compared prostate-specific antigen (PSA) levels in community-based samples of serum from men without prostate cancer. Methods: Japanese-American men aged 40–85 years and native Japanese men aged 40–89 years with no history of prostate cancer provided sera, respectively, in the United States from March 1990 through March 1992 (n = 237) or in Japan from January 1992 through December 1993 (n = 3522). Age-specific PSA levels were used to estimate the prevalences of undetected prostate cancer in the two populations. Results: Age-specific mean PSA levels were significantly lower in Japanese-Americans than in native Japanese (two-sided P<.001). The prevalence of an elevated PSA level increased with age in both populations and exceeded 5% among men aged 60 years or more. Combined with data on prevalence of detected prostate cancer in the two populations, our data suggest that some 10.0% of Japanese-Americans aged 75 years have prostate cancer, with 31% of that fraction remaining undiagnosed. The corresponding estimates in Japan are a total cancer prevalence of 5.4%, of which 81% has not been detected clinically. Conclusions: The total cancer prevalence ratio 10.0/5.4 = 1.9 (95% confidence interval = 1.5–2.3) in Japanese-American men compared with Japanese men in Japan suggests an increased risk for Japanese-American men, but of less magnitude than the fourfold to sixfold increase indicated by the incidence data. [J Natl Cancer Inst 1997;89:1716–20].

Prostate cancer incidence and mortality rates in Japan are lower than the corresponding rates in all other developed countries, including those for Japanese-Americans (1–3). During the period of 1983–1987, the average annual age-adjusted prostate cancer incidence rates were 47.2 and 51.0 per 100,000 for Japanese men in Los Angeles and Hawaii, respectively. These rates are roughly four times higher than the average 12.1 per 100,000 of age-adjusted incidence rates from six regions in Japan during the same time period (1). Prostate cancer incidence has increased from the period of 1983–1987 to that of 1988–1992 in both populations, but the increase in Japanese-Americans is larger; incidence rates in 1988–1992 were 82.4 and 92.8 per 100,000 in Los Angeles and Hawaii, respectively, which are approximately six times higher than the average 13.9 per 100,000 of rates in Japan. In 1983–1987, the age-adjusted mortality rates for prostate cancer (per 100,000) were 9.6 for Japanese in Los Angeles and 3.5 for Japanese in Japan, resulting in a less marked 2.7-fold rate ratio (2,4). All of these rates are adjusted to the age distribution of the 1970 U.S. census population. The higher rates of prostate cancer in Japanese-American men than in native Japanese men have prompted the hypothesis that lifestyle characteristics play a major role in prostate carcinogenesis (5). However, part or all of the increased incidence in Japanese-Americans may reflect more intensive screening in the United States by measurement of prostate-specific antigen (PSA) levels, digital rectal examination, and transurethral ultrasound or more prevalent transurethral resection of the prostate for benign prostatic hyperplasia. Such intensive screening would increase the number of reported cases, some of which might never have been diagnosed otherwise (6). This is plausible because the high prevalence of prostate cancer found incidentally at autopsy or at transurethral resection of the prostate makes the reported incidence rates dependent on the frequency of medical procedures that increase the chance of finding such latent disease (5).

To examine this issue, we compared serum PSA levels in Japanese-American men with those in native Japanese men; the men in both groups had no history of clinical prostate cancer. We used the proportions of these men with elevated PSA levels to obtain estimates of the prevalence of undetected prostate cancer in the two populations. When added to the prevalences of detected cancer obtained from the incidence data cited above, these estimates provide estimates of the total cancer burden among Japanese men in the United States and in Japan.

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See “Notes” following “References.”

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Subjects and Methods

Subjects

Measurements of serum PSA levels in Japanese-Americans were obtained from 237 men aged 40–85 years who had no history of prostate cancer and who participated in a community-based mass screening program for prostate cancer conducted in 22 regions of Gunma Prefecture, Japan, from January 1992 through December 1993. Characteristics of the men and their screening outcomes were reported elsewhere (8). No subjects were excluded because they had benign prostatic hyperplasia, previously undetected prostate cancer, or other pathologic conditions of the prostate identified in the screening program. Protocols in the use of an automated, polyclonal–monoclonal immunochemiluminometric assay formatted for use on the Ciba Corning ACS: 180 system (Ciba Corning Diagnostics Corp., East Walpole, MA) (9). These measurements were converted to Tandem-R monoclonal–monoclonal assay values (Hybritech Inc., San Diego, CA) by use of the equation Tandem-R = 0.556*ACS + 0.038 (R² = .977) obtained by linear regression from a calibration study in the same laboratory.

Serum PSA concentrations among the Japanese-Americans were measured in the laboratory of the Department of Urology, Stanford University, with the use of an automated, polyclonal–monoclonal immunochemiluminometric assay formatted for use on the Ciba Corning ACS: 180 system (Ciba Corning Diagnostics Corp., East Walpole, MA) (9). These measurements were converted to Tandem-R monoclonal–monoclonal assay values (Hybritech Inc., San Diego, CA) by use of the equation Tandem-R = 0.556*ACS + 0.038 (R² = .977) obtained by linear regression from a calibration study in the same laboratory.

Serum PSA concentrations for the men in Japan were measured with the use of Tosoh PSA kits in the laboratory of the Department of Urology, Gunma University. These measurements were converted to the Tandem-R equivalent by use of the equation Tandem-R = 1.0122*Tosoh + 0.1377 (R² = .980) obtained by linear regression in the same laboratory.

Analysis based on the Tandem-R values of a subset of 1647 men whose PSA levels had been measured by both Tandem-R and Tosoh methods gave very similar results (data not shown). These findings indicated that international differences are not confounded by assay differences.

A serum PSA value was categorized as elevated if it exceeded the 95th percentile of PSA levels among those men in the same 10-year age group who showed no evidence of prostate cancer as judged by digital rectal examination and transurethral ultrasound in the same screening program in Gunma Prefecture, Japan (8). We did not have access to the original dataset containing PSA values and results of other screening procedures among the Japanese subjects; therefore, we were unable to address the impact of choosing other cutoff points on our results. The 95th percentile has been used by other authors in their reports of age-specific reference values for serum PSA testing. The age-specific 95th percentile levels used in this study, as well as those in similar groups of U.S. white men, are shown in Table 1 (8,10–12).

Statistical Methods

Previous analyses in U.S. whites and African-Americans suggest that PSA levels in men without clinical evidence of prostate cancer increase exponentially with age (12–14). Accordingly, we used ordinary least-squares regression to estimate the parameters a and b in the relation log(PSA) = a + b*age in each population. We used analysis of covariance to test for differences in age-specific PSA levels between the United States and Japan. We also used logistic regression to evaluate which the prevalence of an elevated PSA varied with age and by country of residence. These statistical analyses were performed with the use of the SAS statistical package (15). All P values resulted from use of two-tailed statistical tests. The prevalence of an undetected cancer was estimated as P = 0.05, as described in the “Appendix” section. The variance of this prevalence (i.e., the variance of P) at a given age was estimated from the covariance matrix of the logistic regression parameters by use of the delta method (16).

We used incidence data to estimate the cumulative risk R of having a clinically diagnosed prostate cancer by specified ages in each of the two populations. Specifically, we took the cumulative risk at the end of the ith age interval to be

\[ R_i = 1 - \exp \left( \sum_{j=1}^{i} r_j \right) \]

where \( r_j \) is the age-specific incidence rate in the \( j \)th 5-year age group. For Japanese-Americans, we used the average of age-specific incidence rates in 1988–1992 from two populations (Los Angeles and Hawaii, provided by A. H. Wu and L. N. Kolonel). For rates in Japan, we used the average of rates from four populations (Hiroshima, Miyagi, Nagasaki, and Yamagata) during the same or overlapping time periods (17); Tsubono Y, Soda M, Sato Y: personal communication). These cumulative risks give the prevalence of having a prior clinically detected prostate cancer among men of various ages. This prevalence was then added to the estimated prevalence of undetected cancer to estimate total cancer prevalence. The variance of the latter was taken to be that of the estimated prevalence of undetected cancer. We obtained confidence intervals for the ratio \( R \) of total cancer prevalence in the United States to that in Japan by using the delta method (16) to estimate the variance of \( \log R \), using a Gaussian approximation to obtain confidence limits for \( \log R \), and then exponentiating these limits.

Results

The 237 Japanese-American men were older at serum collection (mean age = 70.2 years; standard deviation [SD] = 6.7 years) than the 3522 men in Japan (mean age = 65.8 years; SD = 7.8 years) (P<.001). Since PSA levels in healthy men increase with age, we compared PSA levels of the two populations within specific age groups. Fig. 1 shows geometric mean PSA levels for Japanese men in the United States and in Japan, by 10-year age group, with age groups 40–49 years and 50–59 years combined in the United States because of small numbers in the former group. The curves represent the fitted relation \( \text{PSA} = \exp(a + b*age) \), with age measured in years. The parameter estimates (and standard errors [SEs] in parentheses) are \( a = -1.842 (0.695) \) and \( b = 0.028 (0.010) \) in the United States and \( a = -0.988 (0.114) \) and \( b = 0.019 (0.002) \) in Japan. PSA levels increased with age in both countries (P<.01). Apart from the anomalous drop in Japan in the age group 80–89 years, the log-linear relation provides a reasonably good fit to the data. (In neither country did adding a quadratic term to the log-linear regression substantially improve the fit.) Age-specific mean PSA levels were significantly lower in the United States than in Japan (P<.001).

Fig. 2 shows the prevalence \( P \) of an elevated PSA level in each of the two countries. The curve represents the fitted

Table 1. 95th percentiles of serum prostate-specific antigen (PSA) (ng/mL) values among community-based samples of men with no clinical evidence of prostate cancer*

<table>
<thead>
<tr>
<th>Population reference</th>
<th>Japanese men in Japan†</th>
<th>U.S. white men†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Imai et al. (8)</td>
<td>Oesterling et al. (10)</td>
</tr>
<tr>
<td>40–49</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>50–59</td>
<td>2.9</td>
<td>3.0</td>
</tr>
<tr>
<td>60–69</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>70–79</td>
<td>5.2</td>
<td>5.0</td>
</tr>
<tr>
<td>80–89</td>
<td>5.9</td>
<td>NA</td>
</tr>
</tbody>
</table>

*NA = not available.
†Values in columns = serum PSA levels in ng/mL.
logistic relation \( \log[P/(1 - P)] = a + b \times \text{age} \), with age measured in years. The parameter estimates (and SEs in parentheses) are \( a = -4.6477 \ (2.767) \) and \( b = 0.0295 \ (0.039) \) in the United States and \( a = -5.1362 \ (0.584) \) and \( b = 0.0383 \ (0.009) \) in Japan. The prevalence of an elevated PSA level increased with age in Japan \( (P < .0001) \). We found no statistically significant relationship between the prevalence of elevated PSA levels and age in the U.S. subjects \( (P = .44) \) because of the small sample size. There was no statistically significant difference in prevalence of elevated PSA levels between the Japanese-American and native Japanese subjects \( (P = .59) \). In both countries, the prevalence exceeded 5% in all men aged 60 years or more.

In the ‘‘Appendix’’ section, we show that the prevalence \( P \) of an elevated PSA level in a given population of men without clinical cancer is approximately \( P = 0.05 + P_{CA}(1 - d) \). Here \( P_{CA} \) is the true (unknown) prevalence of a prostate cancer sufficiently advanced to produce an elevated PSA, and \( d \) is the proportion of such cancers that are detected clinically. Thus, \( P - 0.05 \) represents approximately the prevalence \( P_{CA}(1 - d) \) of undetected prostate cancer.

Estimated prevalences of undetected and detected cancer are shown in Fig. 3 for each of the two populations. It is evident that undetected cancers comprise most of the cancer burden in Japan, but not in the United States. For example, among men aged 75 years in Japan, the prevalences of detected and undetected cancers are 1.0% and 4.4%, respectively, for a total cancer prevalence of 1.0% + 4.4% = 5.4% and a detection rate of 1.0/5.4 = 0.19. In contrast, the corresponding estimates in the United States are 6.9% and 3.1%, giving a total cancer prevalence of 10.0% and a detection rate of 6.9/10.0 = 0.69. Thus, the ratio of total cancer prevalence in Japanese-Americans aged 75 years compared with Japanese men of this age in Japan is 10.0/5.4 = 1.9 (95% confidence interval = 1.5–2.3). While supportive of an increased cancer prevalence among Japanese-Americans, this ratio is nevertheless smaller than the incidence ratios of 4.1 (i.e., for the period 1983–1987) and 6.3 (i.e., for the period 1988–1992) cited earlier.

**Discussion**

We have used age-specific estimates of the prevalence of elevated PSA levels to estimate the prevalence of undetected prostate cancer in Japanese-American and native Japanese men. The data suggested that prostate cancer detection rates in Japanese-Americans are considerably higher than those in native Japanese men. We found that, among men aged 75 years, some 69% of prostate cancers are detected in the United States, in contrast to only 19% of cancers in Japan. By adding the estimated prevalence of undetected prostate cancer to the prevalence of detected cancer obtained from published incidence data, we calculated that the total cancer prevalence in Japanese-Americans in this age group was approximately 1.9 times that of native Japanese men, in contrast to the fourfold and sixfold incidence ratios.

These findings are consistent with those of Shimizu et al. (6), who estimated the rates that would prevail in Japan if cancers were detected and registered as systematically in Japan as they are in the United States. Using the relative prevalences of cancer at autopsy in the two populations to estimate their relative prevalences of localized cancers, these authors estimated the number of localized cancers that would be registered in Japan if detection rates were similar to those of the United States. When this number was added to the existing counts of aggressive cancers, the resulting total incidence in Japan was three to four times the published incidence, suggesting that most of the incidence differences between Japanese-Americans and Japanese in Japan are due to differences in detection rates.

Age-adjusted death rates from prostate cancer among Japanese-Americans are roughly 2.7 times those among Japanese in Japan. This ratio is larger than our estimated prevalence ratio of 1.9, although it is smaller than the incidence ratios of 4.1 and 6.3. Interpretation of the mortality rate ratio is complicated by possible international differences in cause-of-death certification and coding. In the absence of such differences, the higher mortality rate ratio compared with the prevalence ratio...
of 1.9 would suggest that a higher proportion of prostate cancers are fatal among Japanese-Americans than among native Japanese men.

Our study has some limitations that warrant consideration in interpreting the results. While Japanese-American men comprise an age-stratified random sample of men without clinical cancer, men in Japan were participants in a screening program who could have been self-selected because of prostate conditions. In addition, the sparse numbers of Japanese-American men limit the precision with which mean PSA levels can be estimated. The small sample size of Japanese-American subjects may also explain why we found neither a statistically significant relationship of age and elevated PSA levels in these men nor a statistically significant difference in the proportion of men with elevated PSA levels between the two populations. Furthermore, our estimates of undetected cancer prevalence include only those cancers causing an elevated PSA level, whereas the detected cancer prevalence rates include some cancers still too small to do so. Finally, we have assumed that the age-specific 95th percentiles of PSA levels observed in men without clinical evidence of cancer in Japan are the same as those that would be observed among a similar sample of Japanese-Americans.

These limitations seem unlikely to alter the basic conclusion that PSA levels in a random sample of Japanese-Americans without a clinical history of prostate cancer are lower than those in a comparable sample of Japanese men in Japan. This apparently paradoxical finding is actually what one would expect from more intensive screening for the disease among Japanese-American men than among Japanese men in Japan. Additional com-
parative studies of PSA levels, prostate cancer incidence, and prostate cancer prevalence at autopsy in the two populations are needed to confirm the present findings. If confirmed, these results indicate that the differences in incidence between Japanese-American men and Japanese men in Japan are smaller than implied by incidence data and suggest that the proportion of prostate cancers attributable to environmental factors may be smaller than that previously supposed.

Appendix

The prevalence $P$ of having an elevated PSA level in a population of men of a given age without a clinical history of prostate cancer can be approximated as follows: In a population of $N$ men of the given age, let $P_{CA}$ represent the proportion of men who have developed prostate cancer sufficiently advanced to produce an elevated PSA level. A fraction $d$ of these $NP_{CA}$ cancer cases will have come to clinical attention. These $NdP_{CA}$ men have been excluded from the present study, leaving $N - NdP_{CA}$ men for analysis. By definition of “elevated” PSA level, 5% of the $N - NP_{CA}$ men without prostate cancer have elevated PSA levels. In addition, all of the $NP_{CA}(1 - d)$ men with undetected cancer have elevated PSA levels. Thus, the total number of men with elevated PSA levels is $0.05N(1 - P_{CA}) + NP_{CA}(1 - d)$. The prevalence $P$ of elevated PSA levels is thus

$$P = \frac{\text{(number with elevated PSA)}}{\text{(number analyzed)}} = \frac{0.05(1 - P_{CA})}{1 - dP_{CA}}. \quad [1]$$

When prostate cancer prevalence is small (i.e., $P_{CA} < 0.20$, as is true in these two low-risk populations), then $0.05(1 - P_{CA}) - 0.05$ and $1 - dP_{CA} - 1$. Thus, expression 1 can be approximated by

$$P = 0.05 + P_{CA}(1 - d). \quad [2]$$

The error due to this approximation is practically negligible; e.g., given $P_{CA} = 0.16$ and $d = 0.69$, the prevalence $P$ is calculated as 0.103 by the exact method (expression 1) and 0.996 by approximation (expression 2), respectively. Expression 2 indicates that the excess prevalence $P - 0.05$ is approximately the proportion $P_{CA}(1 - d)$ of men with undetected prostate cancer.

References


Notes

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