Historical Paper

Prostate-specific Antigen Levels and Subsequent Prostate Cancer: Potential for Screening

Kathy J. Helzlsouer,1 John Newby, and George W. Comstock1
Department of Epidemiology, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore 21205 [K. J. H., G. W. C.], and the Washington County Hospital Association, Hagerstown 21740 [J. N.], Maryland

Abstract
Prostate-specific antigen levels are increased in men with prostatic disease, including prostate cancer, and have been used clinically to monitor the response of prostate cancer to therapy. More recently, prostate-specific antigen levels, usually in combination with digital rectal examination or transrectal prostatic ultrasonography, have been suggested to be useful for the detection of prostate cancer. To evaluate the association between a single serum prostate-specific antigen level and the subsequent development of prostate cancer, we measured serum levels in 35 men who donated blood to a community-based serum bank in 1974 and who subsequently developed prostate cancer and in 35 matched controls from the same group of volunteers. Levels of prostate-specific antigen were significantly higher in men who went on to develop prostate cancer, up to 6 years prior to the time of diagnosis in the cases. The level of prostate-specific antigen decreased with increasing time to diagnosis. However, we found no significant relationships between mean levels of prostate specific antigen and survival time (P = 0.632). The sensitivity and specificity of a prostate-specific antigen level ≤ 4 μg/liter up to 3 years prior to the time of clinical diagnosis were both 100% and 87%, respectively. Because prostate-specific antigen levels are relatively insensitive and specific in detecting prostate cancer up to 6 years prior to the time of diagnosis, their use in screening would not improve the sensitivity and specificity of prostate cancer screening. While prostate-specific antigen levels have been used to indicate the presence of prostate cancer, it is not clear whether this level will help patients to detect prostate cancer.

Introduction
It is estimated that prostate cancer will affect 132,000 men and cause 34,000 deaths in the United States in 1992 [1]. This makes prostate cancer the second leading cause of cancer death among men in the United States. Age is the strongest predictor of prostate cancer, with the majority of cases occurring in men over the age of 60, and a median age at diagnosis of 72 years [2]. However, it still remains a significant contributor to premature mortality among men. Based on life expectancy, the average years of life lost per man with prostate cancer is about 9 years [3]. Only 60% of all prostate cancers are localized to the prostate at the time of diagnosis. The extent of disease at diagnosis is a significant prognostic factor, with 5-year survival rates of 80–90% for localized disease at the time of diagnosis [4]. Methods to improve the early detection of the disease should translate into improved survival rates and ultimately decreased mortality from prostate cancer.

PSA is a serine protease secreted by prostatic epithelial cells [5] and has been used clinically to monitor the response of prostate cancer to therapy. Recently, the measurement of PSA levels has been proposed as a means for the early detection of prostate cancer, usually in combination with other modalities such as digital rectal examination and prostatic ultrasonography. Catala et al. [4] reported a sensitivity of 79% and a specificity of 59% for PSA levels ≤ 4 μg/liter among a group of men aged 50 and older who were undergoing prostatic ultrasonography and biopsy of the prostate. The present investigation is a pilot study of the association between PSA levels and the subsequent development of prostate cancer using a population-based serum bank established in Washington County, Maryland, in 1974.

Materials and Methods
Study Population. A nested case-control study was conducted using cases and matched controls from a previous study of prostate cancer in Washington County, Maryland [5]. A blood collection campaign was conducted in 1974 which provided 25,802 specimens for a serum bank (CLUE I). Of the 25,802 persons in CLUE I, 20,305 were identified as residents in the 1975 private census, which had a coverage of approximately 90%. A total of 4,535 white males aged 40 years or older donated blood for the serum bank and were enumerated in the private census. This is a participation rate of 29.3%.

Incident cases of prostate cancer that developed among these volunteers were identified by linking the

Received 3/14/92.
1 Supported by USPHS Grant CA36390.
2 K. J. H. is a recipient of a Preventive Oncology Academic Award from the National Cancer Institute. To whom requests for reprints should be addressed, at the Department of Epidemiology, The Johns Hopkins University School of Hygiene and Public Health, 615 N. Wolfe Street, Baltimore, MD 21205.
3 G. W. C. is a recipient of a Career Research Award from the National Heart, Lung, and Blood Institute.

The abbreviation used is: PSA, prostate-specific antigen.

Reprinted with permission from the American Association for Cancer Research (Cancer Epidemiology, Biomarkers & Prevention, 1992, Volume 1, pages 537–540).
Table 1  Frequency distribution for selected characteristics of cases and controls

<table>
<thead>
<tr>
<th>Age in 1974</th>
<th>PSA cases (n = 35)</th>
<th>Original study (n = 103)</th>
<th>PSA controls (n = 35)</th>
<th>Original study (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>40-54</td>
<td>7</td>
<td>18</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>55-64</td>
<td>8</td>
<td>33</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>65-74</td>
<td>14</td>
<td>43</td>
<td>17</td>
<td>43</td>
</tr>
<tr>
<td>75+</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Years of education</td>
<td>29</td>
<td>85</td>
<td>30</td>
<td>78</td>
</tr>
<tr>
<td>&gt;12</td>
<td>6</td>
<td>18</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Cigarette smoking history, 1974</td>
<td>10</td>
<td>30</td>
<td>9</td>
<td>34</td>
</tr>
<tr>
<td>Never</td>
<td>19</td>
<td>44</td>
<td>17</td>
<td>49</td>
</tr>
<tr>
<td>Current smoker</td>
<td>6</td>
<td>29</td>
<td>9</td>
<td>20</td>
</tr>
</tbody>
</table>

For the original study, controls were selected from the serum bank population and matched to the cases by race, sex, and age, selecting the eligible control who was nearest in age to the cases. Cases included in the study were those diagnosed between 1975 through 1986 and who had no record of any other cancer except for possible nonmelanomatosus skin cancer. The single black case was excluded. Controls were free from known cancer, with the exception of nonmelanomatosus skin cancer, up to the time of diagnosis of the cases.

A total of 103 pairs of cases and matched controls were selected for the study of serum nutrients (5). Because serum from these cases and controls had also been used for other studies, there was sufficient serum from only 35 pairs of cases and controls for this pilot study. Table 1 compares the characteristics of cases and controls from this subset with the original 103 case-control sets.

**Laboratory Assays.** Sera from cases and controls were arranged in paired sets of two, except for eight sets which also included an aliquot of pooled reference serum for quality control. Sera were kept frozen at −70°C aside from having been thawed briefly for two previous studies. After thawing for preparation of aliquots for the present study, the samples were refrozen and delivered to the laboratory. Aliquots within sets were assayed on the same day by the same technician, who was masked to the source of the sera. PSA serum levels were determined by the Tandem-E Immuno-enzymetric assay (Hybritech, San Diego, CA). The coefficient of variation for the eight quality control specimens was 4.8%. The minimal detectable PSA concentration was 0.5 µg/liter.

**Statistical Analysis.** Sensitivity and specificity were calculated considering a PSA level ≥4 µg/liter to be a positive test. PSA levels for cases and control were plotted as a function of time to diagnosis of the cases. The mean serum PSA levels between cases and controls were compared, and the significance of the differences was tested by a paired t test. PSA values were log transformed to normalize the distribution of values. For ease of interpretation, the nontransformed values are presented.

![Sensitivity and Specificity of Serum PSA Level ≥ 4 µg per liter According to Years Until Diagnosis](https://academic.oup.com/aje/article-abstract/168/7/841/82106)

**Fig. 1.** 1974 prostate-specific antigen level by year of diagnosis for prostate cancer cases and their matched controls.
Results

The median age of cases and controls at the time of blood sampling was 67.5 and 67.9 years, respectively. The distributions of selected characteristics among cases and controls are displayed in Table 1.

PSA levels are plotted for cases and controls by year of diagnosis in Fig. 1. The dashed line indicates the cut point of 4 μg/liter for a "positive test," which is commonly cited in the literature. The sensitivity and specificity of a PSA value ≥4 μg/liter up to 6 years prior to the time of diagnosis are 67% and 85%, respectively. Considering only the first 3 years following blood sampling, both the sensitivity and specificity are 75%. It is of interest to note that two controls with 1974 PSA levels of 1.0 and 2.7 μg/liter subsequently developed prostate cancer in 1987 and 1989, respectively.

Table 2 displays the mean PSA levels for cases and controls, grouped by 3-year periods from the time of blood sampling until the year of diagnosis of the case. Cases have significantly higher prediagnostic levels of PSA compared to controls up to 6 years prior to the time of diagnosis of the cases. Mean levels of PSA for the cases tend to be consistently higher than their matched controls up to 12 years from the time of blood drawing, although for groups diagnosed in years 6 through 12 the mean levels are below the cut point of 4 μg/liter. PSA levels among controls decrease from group 1 to group 4, most likely representing an effect of age on PSA levels at the time of blood sampling. The mean age in 1974 for controls in group 1 was 71.6 years compared to mean ages for groups 2 through 4 of 65.6, 55.6, and 57.8 years, respectively. Mean PSA levels increase with increasing age, as shown in Table 3. The slight increase in PSA levels with increasing age observed in this study has also been noted in another study (7).

PSA levels among cases by extent of disease and year at diagnosis are presented in Table 4. For cases developing in the first 3 years following blood collection, PSA levels tended to be lower among those with localized disease than with cases with more extensive disease at diagnosis.

Discussion

Men who developed prostate cancer up to 6 years after blood was drawn had significantly increased prostatespecific antigen levels compared to age-matched controls. As expected for a tumor marker for early detection, the value of a single PSA level determination for detecting disease decreased with increasing time to diagnosis. The sensitivity and specificity of a PSA of ≥4 μg/liter for cases diagnosed within the first 3 years from blood sampling are both 75%. For cases diagnosed within 6 years of blood sampling the sensitivity and specificity are 67% and 85%, respectively. If the definition of a positive result was changed to 6 or more μg/liter, sensitivity for detecting cases diagnosed within 3 years of testing would be 75% and specificity 92%. Even based on a PSA level of ≥4 μg/liter, the time of diagnosis for one-half of the cases (18 of 35) could have been advanced up to 6 years. Whether this advance in the timing of diagnosis (lead time) would translate into an improved survival and reduced mortality from prostate cancer can only be answered in a randomized clinical trial.

Other studies have suggested that PSA determinations, usually evaluated in combination with a digital rectal examination and/or transrectal prostatic ultrasoundography, are useful for the detection of prostate cancer (8–11). Although a study by Perrin et al. (12) concluded PSA alone was of little value as a screening tool, men with PSA levels greater than 4 μg/liter were biopsied only if a digital rectal exam was abnormal. Sixty % of the men with elevated PSA levels had normal prostates on rectal examination and were not further evaluated.

In a screening study of prostate cancer, one concern is whether the cancer detected by the screening method is clinically relevant or represents so-called latent or histological prostate cancers. The term “latent cancer” is used to describe prostate cancer which appears malignant histologically but is unlikely to be a cause of morbidity or mortality. Our study has the benefit of a prolonged period of follow-up (12 years after blood collection) and evidence of complete ascertainment of prostate cancer cases in the cohort. Because of the long follow-up period and the absence of any mass screening program in the community, the cases occurring in the cohort and included in this study are likely to represent clinically relevant prostate cancers. However, since the eight cases diagnosed in the first 3 years with cancer localized to the prostate were diagnosed by transurethral resection, we cannot rule out the possibility that a portion of the cases are of the latent type. On the other hand, the controls during the period of study are likely to be truly negative for clinically relevant prostate cancer.

While the results demonstrate the value of PSA for the detection of prostate cancer, this study fails to address several issues concerning its use as a screening tool for the early detection of prostate cancer. The predictive value of PSA cannot be addressed in this nested case-control study. As with most cancer screening tests, the positive predictive value when used in the general population will be low. Since the majority of prostate cancers occur in men without any known risk factors (13), selective screening based on factors other than age criteria, as in breast cancer, is unlikely to be helpful (14–16). Another central issue of any proposed method of screening is
whether the early detection of prostate cancer results in a reduction of mortality from prostate cancer. This is dependent on the availability and acceptability of effective treatment for prostate cancer as well as the validity, safety, and acceptability of the screening test.

For the near future, it seems likely that prostate cancer screening will be most applicable in the offices of primary care physicians. Availability and acceptability of a screening test is a major factor in deciding on screening methods. Digital rectal examination is available for essentially all male patients in the appropriate age range. A disadvantage is its inability to detect lesions in the anterior portions of the prostate. Assays for PSA are equally available in the office setting through a variety of local, regional, and national laboratories, and their validity is not dependent on the location of the cancer. Transrectal ultrasonography is another potential method for the early detection of prostate cancer. The relatively low sensitivity and specificity of this method for the detection of early prostate cancers (17) as well as the limited availability in the primary care setting may limit its usefulness as a screening test. At present, the combination of PSA assays and digital examinations appears to be an attractive means of screening for prostate cancer in the practitioner's office.

The findings of this pilot study suggest that high priority should be given to the evaluation of using PSA levels in screening for prostate cancer for the young men, specifically as a screening test in preventing prostate cancer mortality. Findings from such a trial should allow rational decisions to be made regarding the desirability of widespread screening.

Acknowledgments

The authors thank Sue Ann Sullivan and Sandy Hoffman for all their help with data retrieval and Allyn Arnold and Gloria Zopp for their help in manuscript preparation. The authors are grateful for the cooperation of all participants of the CLUE I Study in Washington County, Maryland.

References


Table 4 PSA levels in 1974 among cases by extent of disease at diagnosis and time of diagnosis

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>Localized</th>
<th>Regional</th>
<th>Distant</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>X ± SD</td>
<td>No. of cases</td>
<td>X ± SD</td>
</tr>
<tr>
<td>1975–77</td>
<td>8</td>
<td>13.4 ± 12.8</td>
<td>1</td>
<td>38.9</td>
</tr>
<tr>
<td>1978–80</td>
<td>15</td>
<td>9.6 ± 11.6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1981–83</td>
<td>1</td>
<td>2.0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1984–86</td>
<td>1</td>
<td>2.0</td>
<td>2</td>
<td>2.2 ± 2.1</td>
</tr>
</tbody>
</table>