ABSTRACT

Objectives. To evaluate the relationship between low prostate-specific antigen (PSA) levels that are considered normal and the long-term risk of prostate cancer.

Methods. The relative risk of, and cumulative probability of freedom from, prostate cancer by PSA level and age decade was evaluated in male participants of a longitudinal aging study, the Baltimore Longitudinal Study of Aging (National Institute on Aging). The relative risk was estimated from a Cox proportional hazards regression model for men aged 40 to 49.9 (n = 351) and 50 to 59.9 (n = 445). The disease-free probability was determined by Kaplan-Meier survival analysis.

Results. The relative risk of prostate cancer for men aged 40 to 49.9 was 3.75 (range 1.6 to 8.6) when the PSA level was at or greater than the median (0.60 ng/mL) compared with men with PSA levels less than the median. This risk was similar for men aged 50 to 59.9 when comparing those with PSA levels greater than and less than the median (0.71 ng/mL). At 25 years, the cumulative probability of freedom from prostate cancer for men aged 40 to 49.9 was 89.6% (range 81% to 97%) and 71.6% (range 60% to 83%) when the PSA level was less than and greater than the median, respectively. The 25-year disease-free probability for men aged 50 to 59.9 was 83.6% (range 76% to 91%) and 58.9% (range 48% to 70%) when the PSA level was less than and greater than the median, respectively.

Conclusions. The association between the baseline serum PSA level and the subsequent risk of prostate cancer suggests that the biologic events that predispose to prostate cancer begin early in middle age. Men who have baseline PSA levels that are “normal” but reflect a higher risk of prostate cancer may be the most appropriate candidates for future prevention trials. Those men with the lowest risk of prostate cancer on the basis of the baseline PSA measurements are unlikely to benefit from frequent PSA surveillance in an effort to detect prostate cancer early.

Prostate-specific antigen (PSA) has been widely used to screen for prostate cancer during the past decade. An evaluation of population data demonstrates recent declines in prostate cancer mortality; however, it is not clear that PSA testing is responsible for these trends. Nevertheless, PSA testing is associated with an average lead time of 5 to 6 years for prostate cancer detection when a PSA level of 4.0 ng/mL is considered the threshold for diagnosis. PSA levels of 3.5 to 4.0 ng/mL and greater are generally considered abnormal for men between 50 and 70 years old. For younger men, 40 to 50 years old, PSA levels greater than 2.0 to 2.5 ng/mL are considered abnormal.

Gann et al., evaluating a single PSA measurement before 10 years of follow-up in the Physicians Health Study, reported that when compared with men with PSA levels less than 1.0 ng/mL, those men with PSA levels between 2.0 and 3.0 ng/mL were five to six times as likely to be diagnosed with prostate cancer in the next 10 years. The risk beyond this time was not evaluated, and the mean age at the baseline PSA measurement in this study was 63 years. Thus, the long-term risk of prostate can-
cancer in younger men as a function of PSA is unknown.

If serum PSA levels that are considered normal provide predictive information regarding the future risk of prostate cancer, the measurement of the baseline PSA could be useful in identifying men with a higher risk of developing prostate cancer at an early age. To evaluate the long-term risk of prostate cancer among young men with normal PSA levels, we studied male participants who were followed up in a longitudinal study of aging during three decades.

**MATERIAL AND METHODS**

**STUDY POPULATION**

The Baltimore Longitudinal Study of Aging (BLSA) is an ongoing, long-term prospective study of aging conducted by the National Institute on Aging (Bethesda, Md), which has been previously described. Since the inception of the BLSA in 1958, a total of 1665 men and 1019 women have participated in the study for varying lengths of time. The participants in the study return for follow-up visits at approximately 2-year intervals.

Beginning in 1991, prostate cancer diagnoses were confirmed by systematic review of all BLSA medical records, mailed questionnaires, and subject evaluation by a urologist at each visit using digital rectal examination and PSA testing. Since 1991, male subjects in the BLSA have undergone standard transrectal ultrasound-directed prostate biopsy for a PSA greater than 4.0 ng/mL and/or digital rectal examination findings suspicious for cancer. Of 1665 men, 162 (9.7%) have been found to have cancer.

**PSA MEASUREMENTS BY SUBJECT AGE AND FOLLOW-UP**

The serum PSA levels (n = 3820) have been measured in a total of 1054 male BLSA participants either at the time of routine subject visits (since 1991) or using a frozen serum bank for available retrospective samples (before 1991) donated at participant visits. All PSA measurements were performed using a monoclonal immunoradiometric assay (Tandem-R, Hybritech, San Diego, Calif). The stability of PSA in these frozen serum samples stored at −70°C has been previously described.

Of 1054 subjects with a PSA measurement, 143 (13.6%) had a known diagnosis of prostate cancer. The greater proportion of men with a prostate cancer diagnosis in the 1054 subjects with available PSA measurements compared with the overall BLSA cohort (1665 men) is because those with serum available for PSA measurements were more likely to be active participants and therefore subjected to closer surveillance. No PSA testing outside the BLSA visits was used in this analysis.

Eighty-three cancer cases were excluded because the diagnosis of prostate cancer was made before the first available PSA measurement or no PSA measurement was available from when the patients were between 40 and 60 years old. Four hundred twenty-two subjects without prostate cancer were excluded because no PSA measurement was available between age 40 and 60 years. The lack of a serum sample should not have introduced bias, because it is unlikely a relationship exists between the absence of a blood sample in this cohort and the association between the baseline PSA level and prostate cancer development.

After the exclusions, 549 men were included in the final study cohort, and 60 of these men had cancer (10.9%). Fifteen (25%) of the 60 cancer cases were diagnosed in the era before widespread PSA testing began (before 1990). The cancer stage at diagnosis for the 60 cases was known in 31, locoregional in 26, and metastatic in 3. The management of these 60 cases suggests that they were considered significant cancers in that treatment was radical surgery in 16, radiotherapy in 22, and androgen ablation in 5; in 17 cases, the treatment was unknown.

We evaluated the prostate cancer risk over time as a function of PSA level for men who had PSA measurements available at age 40 to 49.9 (n = 351) and 50 to 59.9 (n = 445). The median age, length of follow-up, PSA level, and age at cancer diagnosis for the study subjects are shown in Table I. The follow-up time for the patients with cancer was significantly longer statistically than for those without cancer in the 40 to 49.9-year-old group, but no difference in follow-up time was found between those with and without cancer in the 50 to 59.9-year-old group.

TABLE I. Description of study cohort

<table>
<thead>
<tr>
<th>Study Cohort by Age Decade</th>
<th>Median Age for All Subjects (yr)</th>
<th>Median Follow-up for Those with Cancer (yr)</th>
<th>Median Follow-up for Those Without Cancer (yr)</th>
<th>Median PSA (ng/mL)</th>
<th>Patients with Cancer (n)</th>
<th>Median Age at Cancer Diagnosis (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49.9 (n = 351)</td>
<td>43.6 (23.2–28.7)</td>
<td>14.3 (0.3–37.2)</td>
<td>12.6 (0.2–36.7)</td>
<td>0.60 (0.05–3.9)</td>
<td>29</td>
<td>67.5 (49.0–75.0)</td>
</tr>
<tr>
<td>50–59.9 (n = 445)</td>
<td>52.9 (16.7–30.7)</td>
<td>12.6 (0.2–36.7)</td>
<td>0.71 (0.05–18.9)</td>
<td>29</td>
<td>59</td>
<td>70.3 (54.3–87.5)</td>
</tr>
</tbody>
</table>

Key: PSA = prostate-specific antigen.

Numbers in parentheses are the range, unless otherwise noted.

* Mann-Whitney U test comparing follow-up years between men with and without prostate cancer, P = 0.00 for 40–49.9 years and P = 0.06 for 50–59.9 years.

† Denotes number of patients with baseline PSA in that age decade.

**STATISTICAL ANALYSIS**

A Cox proportional hazards regression model was used to examine the long-term relationship between quartile PSA level and prostate cancer risk. In this analysis, when more than one PSA measurement was available for a subject within an age decade, the earliest measurement was used as the reference or baseline level for determining risk. The relative risk (RR) and 95% confidence intervals were estimated from the Cox regression model with the first (lowest) PSA quartile treated as the reference category.
A Kaplan-Meier survival analysis was performed to estimate the disease-free probability, with time as a function of the baseline PSA level. Noncancer subjects were censored at death or at October 1999. For this analysis, PSA quartiles were combined when no statistically significant difference in RR existed between groups according to the Cox model. The log-rank statistical test was used to compare the Kaplan-Meier survival curves among the PSA groups. The Mantel-Haenszel (log-rank) statistic was used to test the linear trends between the PSA quartile and the risk of prostate cancer.

Statistical analyses were performed using the Statistical Analysis System, version 6.12, for Windows software package (SAS Institute, Cary, NC).

**RESULTS**

**RR ESTIMATES**

The subjects were divided into four evenly sized groups on the basis of the PSA quartiles (Table II). The PSA levels that defined the groups were 0.30, 0.59, and 0.90 ng/mL for men aged 40 to 49.9 and 0.40, 0.70, and 1.4 ng/mL for men aged 50 to 59.9. For men 40 to 49.9 years old with PSA levels of 0.6 to 0.9 ng/mL, the RR of prostate cancer was 7.9-fold (range 1.7 to 35.5) greater and was significantly different statistically from those men with PSA levels of 0.3 ng/mL or less. The RR was similar when the PSA levels were 0.6 to 0.9 ng/mL or more than 0.9 ng/mL.

For men aged 50 to 59.9 with PSA levels of 0.71 to 1.4 ng/mL, the RR of prostate cancer was 4.9-fold (range 1.9 to 12.4) greater and was significantly different statistically from men with PSA levels of 0.4 ng/mL or less. The RR was similar when the PSA levels were 0.71 to 1.4 ng/mL or more than 1.4 ng/mL (Table II).

For men 40 to 49.9 and 50 to 59.9 years old, the RR estimates were not significantly different statistically for the two quartiles greater than and the two quartiles less than the median PSA level (Table II). The RR estimates were therefore re-evaluated by combining the PSA quartiles above and below the median (Table III). The RR for men 40 to 49.9 years old with a PSA of 0.60 ng/mL or greater was 3.7 (range 1.6 to 8.6) compared with those with PSA levels less than 0.6 ng/mL. The RR was 3.5 (range 2.0 to 6.2) when the PSA levels were 0.71 ng/mL or greater for men 50 to 59.9 years old.

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**TABLE II. Relative risk of developing prostate cancer by quartile prostate-specific antigen level**

<table>
<thead>
<tr>
<th>Quartile PSA by Age Decade (ng/mL)</th>
<th>Median Age (yr)</th>
<th>Total Subjects (n)</th>
<th>Patients with Cancer (n)</th>
<th>RR (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49.9 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.30</td>
<td>43.2</td>
<td>88</td>
<td>2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>0.31–0.59</td>
<td>44.0</td>
<td>86</td>
<td>5</td>
<td>3.4 (0.7–17.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>0.60–0.90</td>
<td>43.4</td>
<td>99</td>
<td>11</td>
<td>7.9 (1.7–35.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;0.90</td>
<td>43.7</td>
<td>78</td>
<td>11</td>
<td>7.0 (1.6–31.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>50–59.9 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.40</td>
<td>52.9</td>
<td>114</td>
<td>6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>0.41–0.70</td>
<td>52.7</td>
<td>118</td>
<td>12</td>
<td>2.0 (0.7–5.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>0.71–1.40</td>
<td>52.4</td>
<td>101</td>
<td>17</td>
<td>4.9 (1.9–12.4)</td>
<td>0.00</td>
</tr>
<tr>
<td>&gt;1.40</td>
<td>54.0</td>
<td>112</td>
<td>24</td>
<td>5.5 (2.3–13.6)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

‡ As determined by the Wald chi-square statistic for comparisons between a PSA quartile with the reference (lowest) quartile.

**TABLE III. Relative risk* of developing prostate cancer by prostate-specific antigen level†**

<table>
<thead>
<tr>
<th>PSA by Age Decade (ng/mL)</th>
<th>Total Subjects (n)</th>
<th>Patients with Cancer (n)</th>
<th>RR (95% CI)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49.9 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.59</td>
<td>174</td>
<td>7</td>
<td>3.6 (1.6–8.6)</td>
<td>0.00</td>
</tr>
<tr>
<td>≥0.60</td>
<td>177</td>
<td>22</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>50–59.9 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.70</td>
<td>232</td>
<td>18</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥0.71</td>
<td>213</td>
<td>41</td>
<td>3.5 (2.0–6.2)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

‡ As determined by the Wald chi-square statistic for comparisons between a PSA group with the reference (lowest) group.

* Relative risk estimated by Cox model.

† Comparing men with PSA values greater than and less than the median PSA level at 40–49.9 and 50–59.9 years.

‡ As determined by the Wald chi-square statistic for comparisons between a PSA group with the reference (lowest) group.
pared with those with PSA levels of 0.70 ng/mL or less.

**Survival Analysis**

Kaplan-Meier survival curves based on the presence of a baseline PSA level of less than or greater than the median are shown in Figure 1. At 25 years, the cumulative probability of freedom from prostate cancer for men aged 40 to 49.9 was 89.6% (range 81% to 97%) and 71.6% (range 60% to 83%) when the PSA levels were less than and more than the median, respectively (Fig. 1A). The 25-year disease-free probability for men aged 50 to 59.9 years was 83.6% (range 76% to 91%) and 58.9% (range 48% to 70%) when the PSA levels were less than and more than the median, respectively (Fig. 1B). The survival curves began to differ 15 years after the baseline PSA for men aged 40 to 49.9 and 10 to 15 years after the baseline PSA for men aged 50 to 59.9. The log-rank test demonstrated a statistically significant linear trend between the PSA quartile and prostate cancer risk for men aged 40 to 49.9 (chi-square test = 9.8, \( P = 0.00 \)) and men aged 50 to 59.9 (chi-square test = 22.4, \( P = 0.00 \)).

**COMMENT**

We have shown, for the first time, the long-term risk of development of prostate cancer in young men during two to three decades as a function of the PSA level. The increased risk of prostate cancer in men aged 40 to 49.9 and 50 to 59.9 with the highest (albeit “normal”) baseline PSA levels becomes evident after 10 to 15 years of follow-up, and was surprisingly similar when the PSA levels were in either of the two quartiles above the median (Table II). Thus, young men with PSA levels around 1.0 ng/mL are at a similar risk of developing prostate cancer as those with PSA levels greater than 2.0 ng/mL, and those at the lowest risk have PSA levels below the median level for that age decade (0.6 to 0.7 ng/mL). To place this risk into perspective, the threefold to fourfold greater risk of prostate cancer development for men in this study with baseline PSA levels greater than the median is more than the twofold increased risk of prostate cancer in a man who has an affected first-degree relative with prostate cancer\(^9\) and is greater than the twofold to threefold increased risk of breast cancer for a women who has 2 first-degree relatives with breast cancer.\(^10\) Therefore, the long-term risk of prostate cancer in men with PSA levels that are “normal,” but higher than the median for a given age decade, is substantial when compared with the risk conferred by a family history of cancer.

The biologic basis for the relationship between the baseline PSA level and the subsequent risk of prostate cancer is not known. Since the progression of prostate cancer is thought to be a slow process, one could speculate that those men with the higher PSA levels are more likely to harbor a premalignant lesion or a small prostate cancer that progresses to become clinically apparent decades later. Fowler et al.\(^11\) recently reported that 1.5% of men without prostate cancer on needle biopsy of the prostate who had a PSA level less than 1.0 ng/mL had high-grade prostatic intraepithelial neoplasia (PIN) compared with approximately 9% of those with PSA levels between 1.0 and 10.0 ng/mL. The finding that high-grade PIN is six times more prevalent on the biopsies of men with PSA levels greater than 1.0 ng/mL than on the biopsies of those with PSA levels less than 1.0 ng/mL is of particular interest in light of our findings, because high-grade PIN is considered a precursor of prostate cancer. It is possible that the presence of high-

![Figure 1. Kaplan-Meier survival curves for men aged (A) 40 to 49.9 years and (B) 50 to 59.9 years. Ninety-five percent confidence intervals are shown at 10 and 20 years. Markers represent prostate cancer cases. \( P = 0.00 \) for men aged both 40 to 49.9 years and 50 to 59.9 years according to the log-rank test. Log-rank test for linear trend was 9.8 for men aged 40 to 49.9 years (\( P = 0.00 \)) and 22.4 for men aged 50 to 59.9 years (\( P = 0.00 \)), both according to the chi-square test.](https://example.com/figure1.png)
grade PIN—a lesion that disrupts the basal cell layer—could cause leakage of PSA into the circulation and result in higher (albeit “normal”) PSA levels for those men who harbor this lesion compared with those without PIN. Another explanation for our findings is that the presence of prostatic inflammation in young men disrupts the prostatic architecture, resulting in relatively higher PSA levels and a greater risk of prostate cancer later on. It has been suggested that inflammation and resultant oxidative stress could be a risk for later development of prostate cancer. Finally, the association between PSA and a later risk of prostate cancer may reflect greater androgen production or action in young men at the highest risk of the disease. PSA is an androgen-dependent gene, and androgen action over long periods is thought to be associated with the development of prostate cancer.

Gann et al. described the risk of prostate cancer development during the 10 years after donation of a single serum sample that was used to measure PSA. The mean age at the baseline PSA measurement in this study was 63 years. They found an increased risk of prostate cancer, fivefold to sixfold higher for men with PSA levels between 2.0 and 3.0 ng/mL compared with men with PSA levels less than 1.0 ng/mL. Our findings for men younger than 60 years at their baseline PSA measurement are consistent with the findings of Gann et al.4 However, our study is unique in the evaluation of prostate cancer risk beyond 10 years in men with low PSA levels at younger baseline ages (40 to 60 years).

There are several important implications of our findings. First, that PSA levels are higher in men who are destined to develop prostate cancer more than a decade before the diagnosis suggests that the pathologic processes leading to prostate cancer begin in early middle age. Thus, any intervention designed to prevent the development of prostate cancer, or alter the progress of this disease, should begin in young men. Second, the relationship between PSA and a later risk of prostate cancer should be useful in the design of future prostate cancer prevention trials. A prevention trial that decreases the androgenic stimulation of the prostate using finasteride is underway, and a trial to assess the value of selenium and tocopherols is being designed. On the basis of our findings, the PSA level could be used as a measure of risk to select a cohort with an increased event rate (development of prostate cancer over time), and this could decrease both the number of men and the time necessary to demonstrate an effect from interventions designed to prevent prostate cancer. Third, although PSA is widely used to screen for prostate cancer, evidence is available that the standard approach—annual testing beginning at age 50 years—is not the most effective screening strategy.4 We have shown that a baseline screen at age 40 years and again at age 45 years, followed by biennial screening after age 50, prevents more prostate cancer deaths and uses fewer resources compared with the standard strategy. The current study provides further data to support the concept that young men who maintain low PSA levels need infrequent testing because of a low risk of prostate cancer development. An approach to screening that uses PSA to stratify risk and thereby determine the appropriate intensity of screening seems more rational that the “one size fits all” approach that is used most commonly today.

Several limitations of our study deserve mention. First, the PSA levels were measured from frozen serum samples, and this could have affected the results. However, in a prior study, we found that the length of storage of serum samples had no significant affect on the PSA level. Furthermore, our median and range for PSA values at each decade on these frozen sera were similar to those of a community-based cohort. Second, the number of cancer cases in our study was relatively small. However, our confidence limits around the estimates of risk (Table III) were similar to those reported from a study with a larger sample size. Finally, the male subjects in the BLSA are primarily white. Thus, our results may not reflect the long-term risk of prostate cancer among other races.

In summary, the relationship between the baseline serum PSA levels and the later risk of prostate cancer suggest that the initial events resulting in prostate cancer development begin in early middle age. Thus, interventions designed to prevent prostate cancer development or progression are more likely to be successful if begun early. The measurement of baseline PSA at an early age may be useful to select men for prevention trials and to determine the appropriate intensity of surveillance for those men interested in the early detection of prostate cancer.

REFERENCES


