PSA Quo Vadis? It Is Reasonable to Start with Prostate-Specific Antigen Testing at the Age of 40!

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Abstract

Background: It is common to start with PSA (prostate-specific antigen)-testing at the age of 50. If patients with a PSA value greater than 4 ng/mL should be considered for prostate biopsy, approximately 20% of all men undergoing test are considered for biopsy at the time of first early-detection examination.

Methods: We have screened 2,592 asymptomatic men younger than 45 years. With a short questionnaire, we assessed age, body mass index (BMI), concomitant diseases, last sexual intercourse, and last bicycle riding. We compared this cohort with a group of 11,656 men aged 45–75 years from a nationwide prostate cancer screening trial.

Results: In this cohort, only 4 men with a PSA value greater than 4 ng/mL and 10 with a PSA greater than 3 ng/mL were identified. More than 99% of all men younger than 45 years had a PSA lesser than 4 ng/mL. Sexual intercourse, bicycle riding, or BMI had a significant but minimal influence on the PSA value.

Conclusions: It is reasonable to start with PSA testing at the age of 40 years. The advantage of screening younger patients is that almost no one should be considered for biopsy at the time of first early-detection examination. We identified a baseline value at which only a minimal influence was exerted by benign prostatic hypertrophy. In comparison with many current guidelines, we gained a lead time of 10 years for observation of PSA dynamics.

Impact: The importance of PSA velocity for stratification of patients at risk for development of significant prostate cancer will grow.

Introduction

In Germany, over 58,000 cases of prostate cancer are diagnosed each year and, while accounting for 25.4% of all cases of cancer, it is the most common type of malignant neoplasms in the male. Among the fatal types of cancer, prostate cancer ranks third with a rate of 10.1% (approximately 12,000). By the year 2050, the proportion of men in Germany aged over 60 years will have risen to 28 million (37%) and will hence be twice the current figure (1). In tandem with that development, a commensurate increase is expected in the number of cases of prostate cancer. The growing demand for diagnosis and treatment of prostate cancer resulting from that demographic trend must be borne in mind.

The initial findings of 2 large randomized controlled clinical trials, known as the European Randomized Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal and Ovary (PLCO) studies, were published in 2009. The ERSPC study showed a 20% decrease in mortality in the PSA screening group compared with the control group (2). In mathematical terms, this corresponds to a reduction from around 3% to 2.4% in the individual risk for a man to die of prostate cancer. During the, still short, median 9-year observation period, 1,410 men underwent PSA screening and treatment was needed for a further 48 prostate cancer patients to prevent, in statistical terms, 1 case of death due to prostate cancer. Presumably due to the fact that, because of the methodology employed, a high number of PSA measurements was carried out in the control group, the PLCO study was unable to identify any PSA-mediated reduction in mortality (3). To be borne in mind, at present, is that the effectiveness of screening for prostate cancer has not been definitively shown. However, there is a widespread consensus that men who wish to engage in early detection of prostate cancer based on PSA test and DRE (digital rectal examination) should not be denied that request (4).

The initial euphoria has evaporated in recent years and the benefits of population- and PSA-based early detection...
is the subject of controversial discussion. Stamey has questioned the correlation between PSA and the presence of prostate cancer, which has continued to decline over the past 20 years (5). In the United States, 226 out of 100,000 men over the age of 65 years die from prostate cancer. However, because autopsy has revealed that up to 80% of 70-year-olds suffer from latent prostate cancer, he fears that the number of clinically insignificant cancers diagnosed will increase (6). On the contrary, other authors believe that the importance ascribed to the correlation between PSA and prostate cancer will decrease in favor of the prostatic volume, because at present it is typically small organ-confined tumors that are being detected. But the challenge faced by early detection lies in ensuring that tumors are neither detected too early (overdiagnosis) nor too late, so that patients can be offered curative treatment (7).

Early detection of prostate cancer must take account of the following 3 problems

1 Curative treatment of prostate cancer is possible only when detected at an organ-confined stage (8). Because prostate cancer becomes evident only at an advanced, mainly metastasized, stage due to the clinical symptoms, early detection must be able to detect this earlier while still at an organ-confined stage. Otherwise, patients would progress despite aggressive treatment aimed at a cure.

2 A special feature of this tumor entity is its onset as a latent and insignificant tumor that has no deleterious effect on the patients during their lifetime. Such tumors should remain undetected because any therapeutic measures taken for these patients would amount to overtreatment.

3 Left untreated, prostate cancer embarks on a slow natural course, hence only men with a life expectancy of 10 to 15 years would benefit from curative treatment (9).

As can be clearly inferred from the above figures, 20% of all men’s condition is identified already during the first early-detection examination. The aim of the present study was to identify the age at which early-detection measures should be initiated, so that as far as possible only normal PSA values would be measured during the first examination.

Materials and Methods

Two patient collectives were investigated for the present study

Screening collective. PSA screening was conducted for 3,930 asymptomatic men aged 25 to 65 years. Patients were recruited through the occupational physicians of large companies so as to assure a high proportion of men younger than 45 years. All men received detailed information about the intended measures and gave their written consent. A blood sample was taken from all men for determination of the PSA value. The samples were centrifuged immediately after collection, stored at 4°C, and measured within 24 hours in our own central laboratory (Hybritech). By using a questionnaire, the patients’ age, height, weight, and details of any concomitant diseases or history of previous urological conditions were recorded. Men were also asked whether they had ejaculated, or had engaged in bicycle riding for at least 30 minutes, during the previous 24 hours. Digital rectal examination was omitted.

Early-detection collective. An early-detection study conducted by ourselves throughout Germany with 11,565 men aged 45 to 75 years served as a comparative (reference) collective. In that study, after informing participants about the nature of the trial, an early-detection examination with withdrawal of a blood sample for determination of the PSA value was carried out. Samples were centrifuged, stored at 4°C, dispatched to the central laboratory, and measured within 48 hours (Hybritech). The data collected were entered into a database. The nonparametric rank sum test based on the Mann-Whitney U test or Pearson’s correlation was carried out for statistical analysis.

Results

Screening collective

In the screening collective investigated, 2,592 men were younger than 45 years and 1,338 older than 45 years. The mean PSA values were 0.69 ± 0.47 ng/mL and 1.01 ± 1.18 ng/mL and differed significantly (P < 0.001). In the under 45-year-old group, significantly higher PSA values (P = 0.045 or P < 0.001) were detected following bicycle riding or ejaculation. The PSA values for men after bicycle riding or ejaculation were 0.73 ± 0.45 ng/mL and 0.71 ± 0.43 ng/mL, respectively. The values for men without previous bicycle riding or previous ejaculation were 0.69 ± 0.47 ng/mL and 0.68 ± 0.48 ng/mL, respectively.

In this collective, too, a significant correlation was identified between the PSA value and body mass index (BMI; P = 0.041).

Among the men younger than 45 years, 15.0% (389/2,592) had a PSA value greater than 1 ng/mL, 1.8% (46/2,592) a PSA value greater than 2 ng/mL, 1.2% (30/2,592) a PSA value greater than 2.5 ng/mL, 0.4% (10/2,592) a PSA value greater than 3 ng/mL, and 0.2% (4/2,592) a PSA value greater than 4 ng/mL (Fig. 1B).

Among the men older than 45 years, 33.9% (453/1,338) had a PSA value greater than 1 ng/mL, 10.6% (142/1,338) a PSA value greater than 2 ng/mL, 6.6% (88/1,338) a PSA value greater than 2.5 ng/mL, 4.3% (58/1,338) a PSA value greater than 3 ng/mL, and 2.7% (36/1,338) a PSA value greater than 4 ng/mL.

Table 1 summarizes mean, median, and range of PSA stratified by age for the screening collective. The
The proportion of men with a PSA value less than 2.5 ng/mL begins to drop starting at the age of 46 years. A similar decrease is observed for the proportion of men with a PSA value less than 1 ng/mL.

**Early-detection collective**

For the men who presented for early detection of prostate cancer, the lower age range was 45 years and the upper age range was 75 years. The mean PSA value was 4.29 ± 1.71. A PSA value greater than 2 ng/mL was measured for 35.2% of men, a PSA value of greater than 2.5 ng/mL for 30.1%, a PSA value of greater than 3 ng/mL for 23.5%, and a PSA value of greater than 4 ng/mL for 17.3%. The PSA value was lesser than 2 ng/mL for 64.8% of men (Fig. 1B). In this collective, no data were recorded on bicycle riding, weight, or ejaculation.

**Screening and early-detection collective**

Figure 2 shows the incidence of men with a PSA value greater than 4 ng/mL in accordance with age. Here the

### Table 1. Analysis of subgroups by age for the screening collective: the table shows mean, median, and range of PSA stratified by age and the proportion of men with PSA values less than 1 ng/mL and less than 2.5 ng/mL, respectively

<table>
<thead>
<tr>
<th>Age, y</th>
<th>N</th>
<th>Mean (ng/mL)</th>
<th>Median (ng/mL)</th>
<th>Range (ng/mL)</th>
<th>n &lt; 2.5 ng/mL (%)</th>
<th>n &lt; 1 ng/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24</td>
<td>30</td>
<td>0.53</td>
<td>0.39</td>
<td>0.26–1.18</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>25–30</td>
<td>384</td>
<td>0.63</td>
<td>0.60</td>
<td>0.14–1.85</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>31–35</td>
<td>536</td>
<td>0.67</td>
<td>0.62</td>
<td>0.17–2.56</td>
<td>99</td>
<td>85</td>
</tr>
<tr>
<td>36–39</td>
<td>828</td>
<td>0.70</td>
<td>0.58</td>
<td>0.10–3.47</td>
<td>98</td>
<td>87</td>
</tr>
<tr>
<td>40–45</td>
<td>814</td>
<td>0.74</td>
<td>0.61</td>
<td>0.09–6.12</td>
<td>99</td>
<td>81</td>
</tr>
<tr>
<td>46–49</td>
<td>442</td>
<td>0.80</td>
<td>0.62</td>
<td>0.14–6.28</td>
<td>96</td>
<td>78</td>
</tr>
<tr>
<td>50–55</td>
<td>564</td>
<td>1.12</td>
<td>0.87</td>
<td>0.07–6.95</td>
<td>92</td>
<td>61</td>
</tr>
<tr>
<td>≥56</td>
<td>332</td>
<td>1.39</td>
<td>0.89</td>
<td>0.07–15.3</td>
<td>90</td>
<td>58</td>
</tr>
</tbody>
</table>
proportion of men younger than 45 years are depicted as belonging to the screening collective and the men older than 45 years are assigned to the early-detection collective. Virtually no men below the age of 42 years had a PSA value greater than 4 ng/mL, but the proportion of such men rose to about 30% up to the age of 75 years (Fig. 2).

In the screening collective, the PSA values are available for patients aged 45 to 65 years. Figure 3 compares the PSA values in the age groups of the 2 collectives (Fig. 3). A PSA value that was higher by 0.27 to 0.66 ng/mL was seen in all age groups of the early-detection collective.

Discussion

In the past, most specialist societies recommended early-detection examination with a PSA test as from the age of 50 years, or a few years earlier if there were any familial risks or for particular races. The problem with that recommendation is that almost 1 out of every 5 men of that age group has a PSA value greater than 4 ng/mL. In recent years, a clear trend has been discernible, whereby a punch biopsy was being offered already to men with a PSA value well below the threshold value of 4 ng/mL. A threshold value of 2.5 ng/mL in our early-detection collective would mean that almost 1 out of every 3 men would have an abnormal result at the first early-detection examination and would require further invasive diagnostic measures. Lowering the threshold age for early detection to 40 years would mean that virtually no man would have an abnormal result at the time of the first examination. That could help men to overcome any anxieties about the initial early-detection examination and improve acceptance of early detection.

In the screening collective, we can observe a distinct rise of the number of men with a PSA value greater than 1 ng/mL or 2.5 ng/mL, respectively. Although the risk of prostate cancer at 40 years of age is low, there are a number of other advantages in beginning early detection before 50 years.

Among younger men, the proportion of cases of benign prostatic hypertrophy (BPH) linked to the PSA value is lower and hence more specific to tumor detection (10).

A baseline PSA value above the age-adjusted median is a better predictor of a future risk of prostate cancer than are familial risk or adherence to a particular race (11, 12). Initiation of early detection at 40 years would therefore obviate the need for making a distinction based on risk groups.

Men in their forties with a PSA value greater than 0.6 to 0.7 ng/mL are at increased risk for prostate cancer. In that manner, risk-adapted screening intervals could be selected (11, 12). In our own screening collective around two-thirds of all men had thus a low risk and could be seen at longer intervals. The Ross and colleagues working group were able to show that by adopting such an approach not only could costs be cut but mortality could also be reduced compared with early detection as from 50 years (13). Reduced mortality is attributable, first, to the fact that on comparing younger men with those over 50 years, the younger men have a higher probability of having a curable form of prostate cancer (14, 15). Second,
analysis of the SEER (Surveillance Epidemiology and End Results—U.S. programme that provides information on cancer statistics) data has revealed that the age-adjusted mortality rate for prostate cancer among men aged between 55 and 64 years is 18 per 100,000 men (16). In view of the fact that the interval between diagnosis of a locally confined prostate cancer and the time of death is around 15 to 20 years (17, 18), these patients could only benefit from early detection before the age of 50 years if they are diagnosed and undergo curative treatment.

Taking these factors into account, German and American specialist societies have decreased the age for recommending an early-detection examination with a PSA test from the age of 50 years down to 40 years (19, 20).

By engaging in PSA measurement at a younger age, a markedly more homogeneous PSA range is obtained for all patients. This could help improve the usefulness of the PSA kinetics. The National Comprehensive Cancer Network recommend the first early-detection examination with a PSA test at the age of 40 years. In this case, a low and homogenous PSA value is very important, because this guideline arrogates a prostate biopsy if PSA kinetics are greater than 0.35 ng/mL/year (21). Bill-Axelson and colleagues (22), more than 70% of patients survived the first 10 years without any evidence of remote metastasization. A lead time of 10 years, during which the PSA-value trend can be monitored, could be gained by reducing the age of initiation of early detection to 40 years. It is well known that there is a relationship between PSA velocity and death due to prostate cancer decades later (23). A baseline PSA value in combination with the extra observation time gained could possibly help to differentiate, on the basis of the PSA trend, between life-threatening prostate cancer that requires treatment and cancer that does not need treatment.

Although the differences in PSA values for young men after ejaculation or bicycle riding are significant, they account for less than 0.1 ng/mL. These differences are of no significance in early detection. The same holds true for the positive correlation with the BMI. These factors need not be taken into account either in early detection as from 40 years.

Figure 3 highlights the differences between the screening and early-detection collectives. In the age range of 45–64 years, men in the early-detection collective can be seen having a higher PSA value than in the screening collective. That difference cannot be explained by the prolonged 48-hour period elapsing before measurement of the samples. PSA is a stable analyte. No relevant loss was seen for PSA samples kept for 24 hours regardless of the storage conditions. After centrifugation, the PSA in the serum continues to be virtually constant at room temperature for 48 hours (24). The more plausible explanation is that the early-detection collective represented a biased group of men who had presented for early detection on their own initiative ("opportunistic screening"): Such men often already have urinary obstructive symptoms. Nonetheless, the differences do not seem to be very important.

Conclusion

It is advisable that PSA-based early detection be initiated at the age of 40 years. One major advantage is that punch biopsy of the prostate would not be indicated for almost any man at the time of the first early-detection examination. One would obtain a baseline PSA with only minimal number of cases of BPH. That would be a good predictor of the future risk of prostate cancer and would allow for a risk-adapted screening interval. Moreover, compared with early detection starting at 50 years, a 10-year lead time (observation period) would be gained and a homogeneously lower baseline PSA obtained. That means that prostate cancer could be detected in young men already at a stage when it is amenable to curative treatment. Furthermore, the possibilities of identifying, on the basis of the PSA dynamics, treatment-requiring prostate cancers would be enhanced.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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