

CORRESPONDENCE

Clinical Application of Ultrasensitive Prostate-Specific Antigen Assays

Junker et al. (1) measured prostate-specific antigen (PSA) levels in sera of subjects who underwent cystoprostatectomy for bladder cancer. Their aim was to establish baseline levels of PSA following prostate removal in patients who do not have prostate cancer. They calculated the "biological lower detection limit," defined as PSA concentration detected in PSA-free human serum plus 3 standard deviations (SDs). This value was 0.29-0.63 ng/mL, and they concluded that ultrasensitive PSA assays have negligible advantages in monitoring patients with prostatic carcinoma. This conclusion is erroneous and is not supported by many other reports in the literature that were not cited by Junker et al.

1) Ultrasensitive PSA assays with detection limits of 0.01-0.001 ng/mL (2-4) allow accurate measurement of PSA levels at very low concentrations.

2) The term "biological detection limit" (5) is used inappropriately, since the definition of Junker et al. matches a parameter proposed by Stamey (6), which is known as "residual cancer detection limit" (RCDL).

3) Prestigiacomo and Stamey (4) and Stamey (6) calculated RCDL to be 0.05-0.07 ng/mL. The values quoted by Junker et al. are fourfold to sixfold higher.

4) After radical prostatectomy, 60%-80% of patients have PSA levels lower than 0.01 ng/mL and as many as 20% have PSA levels lower than 0.001 ng/mL (2,3,7). The merits of ultrasensitive monitoring have been clearly documented (4,7). Changes in PSA levels between 0.001 and 0.1 ng/mL are clinically important (8).

5) Junker et al. attempted to explain their results by speculating that there may be cross-reacting substances, including kallikreins, in serum. These pro-

posals are not correct, since the PSA levels are lower than 0.01 ng/mL in the majority of serum samples from females and prostatectomized males (3,7-9). Junker et al. claim that PSA may be produced by peripheral blood cells and other tissues. The cited papers did not demonstrate PSA protein production by such cells but describe the presence of traces of PSA messenger RNA, detected by polymerase chain reaction (10,11). The literature on nonprostatic PSA (12) does not support the contribution of other tissues to serum PSA. Junker et al. mention the periurethral glands as possible contributors to serum PSA, but Oesterling et al. (13) concluded that the periurethral glands do not significantly influence serum PSA levels.

Why did Junker et al. calculate much higher RCDLs? Cystoprostatectomies in France may be performed differently from those in the United States, which would result in residual prostatic tissue. More likely, the discrepancies originated from the inability of the methods used to discriminate accurately PSA levels below 0.05 ng/mL. The imprecision at such PSA levels will result in high SDs, and the RCDL will be unrealistically high when the mean is added to 3 SDs. RCDL becomes lower as the methods used for PSA become more sensitive (4).

Ultrasensitive PSA assays with biological detection limits of 0.01 ng/mL or lower detect relapse at least 1 year earlier than assays with biological detection limits around 0.1 ng/mL (4,7,8). Recently, it has been shown that initiation of early radiotherapy due to isolated elevation of serum PSA levels following radical prostatectomy significantly improves patient outcomes (14).

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Notes

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Response

We thank Dr. Diamandis for his comments and welcome the opportunity to respond to the points raised.

1) The coefficients of variation of the ultrasensitive assays cited by Diamandis were inconsistent and as large as 67% (1-3). In an article published in 1995, Diamandis and co-workers (4) stated, "any PSA value $<0.020 \mu\text{g/L}$ was considered nonquantifiable by the assay because the precision at lower values was $>20\%$."

2) The determination of the biological lower detection limit in our study was based on PSA measurement in bladder cancer patients after radical cystoprostatectomy in whom prostate cancer had been histologically excluded. Therefore, our definition does not match that of Stamey (5).

3) It is important to stress that we focused on commercially available, ultrasensitive PSA assays. We obtained our results by measuring serum levels under routine laboratory conditions, including internal and external controls.

4) Up to now, positive predictive values for ultrasensitive PSA measurement have not been evaluated. Moreover, in the retrospective studies cited, prostate cancer relapse was defined solely as an increase in PSA levels by use of cutoff levels mostly above the ultrasensitive range (3,4,6).

5) In the study by Oesterling, Diamandis, and co-workers (7), PSA values in patients after cystoprostatectomy and urethrectomy were compared with those in patients after cystoprostatectomy alone. PSA values in this study ranged from 0.0 to 0.31 ng/mL which is in close agreement with our results. Differences in PSA levels between the patient groups were statistically significant as judged by use of two of three assays [$P<.003$; rank sum test, two-sided (7)]. This study did not exclude the contribution of periurethral glands to PSA levels within the ultrasensitive range. In addition, two reports (8,9) exist of presentation of PSA by peripheral blood cells.

One of the reports cited by Dr. Diamandis showed that it may be useful to initiate radiotherapy in prostate cancer patients on the basis of elevated PSA levels alone. This report, however, men-

tioned a cutoff level of 0.4 ng/mL, which is well above the ultrasensitive range (10).

We conclude that ultrasensitive PSA measurements should be treated with caution, since there are obviously men without a prostate who had never had prostate cancer showing PSA levels above the ultrasensitive range.

Like Dr. Diamandis, we can only speculate about the situation in France, but we would expect similar findings there.

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Re: Neuroblastoma Screening Test May Do More Harm Than Good

Mass screening of infants for the early detection of neuroblastoma was started in Japan in the early 1970s, and more than 1 million Japanese children are tested every year (1). The results show that neuroblastoma can be diagnosed early by detecting urinary catecholamine metabolites. The main questions remain, however: 1) Does screening influence mortality? 2) What is the optimal procedure? Fundamental to these questions is to what extent favorable neuroblastoma progresses to unfavorable disease.

The Journal commented recently on a study (2) carried out in the province of Quebec in Canada and published in *The Lancet* (3). The two-step test procedure was scheduled for infants at 3 weeks and 6 months of age. There was no stopping rule on overdiagnosis. The authors reported a 2.4-fold increase in neuroblastoma incidence in the screened population compared with the nonscreened population controls and no reduction of advanced stage disease in older children in the screened cohort. Data were not given on relevant biologic prognostic factors, MYCN copy number (4), aberrations of chromosome 1p (5), and DNA ploidy (4). The authors concluded that

the implementation of screening is not to be recommended. Whether screening in general, especially after 6 months of life, is an approach to lower the mortality from neuroblastoma cannot be concluded from these results.

These results were predicted (6) and known (7) during the planning of the German Neuroblastoma Screening Project initiated in May 1995 as a nationwide, controlled trial to evaluate the influence of screening children at 12 months of age on reduction of advanced stage disease and subsequently neuroblastoma mortality. Preliminary data obtained from the German pilot studies also suggested that a substantial proportion of biologically unfavorable cases can be diagnosed by screening (8) and that overdiagnosis may be reduced at 12 months (9). Screening takes place in six of 16 German states, whereas the remaining states serve as controls. Approximately 1 250 000 children at 12 months of age will be tested during the study period, and the same number will be followed without screening. This large number is needed to achieve sufficient statistical power.

Germany is an ideal candidate for the evaluation: 1) No additional infrastructure is needed to contact the children because of the well-accepted German Medical Prevention Program for Chil-

dren that is offered to all German children (compliance >90%). 2) Children with neuroblastoma from both groups are registered in the German Children's Cancer Registry and are treated according to recommendations of a National Neuroblastoma Treatment Protocol.

In contrast to the Quebec study and the Japanese trial, a clear stopping rule to avoid overdiagnosis has been defined, supervised by the registry. The study is funded by the German Cancer Aid Foundation [not the Federal Government as stated in (2)!] and German health insurance institutions. The all-inclusive costs are less than 10 U.S. dollars per child. The project is designed to provide conclusive results for children screened at 1 year of age.

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Written on behalf of the German Neuroblastoma Screening Project.

Supported by grant M 83/94 from the German Cancer Aid Foundation, Bonn, Germany.