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Age-Specific Reference Ranges for Prostate-Specific Antigen as a Marker for Prostate Cancer

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Abstract

More than a decade ago, several investigators found serum PSA levels in cancer-free men to correlate directly with age and prostatic volume. This provided the basis for the establishment of age-specific reference ranges for PSA constituting an attempt to improve sensitivity and specificity of serum PSA as a marker for prostate cancer. Differing age-specific reference ranges for PSA were established in whites, African Americans, Asians, and Orientals. Moreover, since the introduction of different molecular forms of PSA with the inherent capability to differentiate between benign and malignant disease, age-specific reference ranges for free and complexed PSA have also been established. Subsequent studies sought to evaluate whether the standard 4.0 ng/ml cutoff should be replaced by age-adjusted cutoffs. Multiple trials involving various test modalities yielded inconclusive results. More recently, attempts were made to integrate principles of PSA density and PSA velocity into concepts of age-adjusted cutoffs for PSA envisioning more sensitive and specific PSA driven screening regimens. Hypothetical approaches involving age in association with prostatic growth or longitudinal data of PSA changes in individual men await further evaluation in prospective clinical trials. In conclusion, the usefulness of age-specific PSA ranges remains controversial because of concerns that the use of age-adjusted cutoffs for counselling men to undergo prostate biopsy runs the risk of missing a high proportion of clinically significant cancers in older men and augments the rate of unnecessary biopsies in younger men.

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1. Introduction

Since the introduction of PSA testing for prostate cancer screening there has been realized a downward shift from advanced incurable cancer to organ-confined disease. Nonetheless, the diagnostic usefulness of serum PSA especially in mass screening is a matter of debate. For it has been recognized since the early 1990s the PSA test produces up to 70% false positive results peaking in men beyond their fifth decade of age [1]. Moreover, data from the European randomized study of screening for

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prostate cancer (ERSPC) indicate that the positive predictive value of PSA as a screening test is discontenting 30% [2]. Other investigators reported only 17% positive predictive value for PSA alone and an increase to 51% when applied in combination with digital rectal examination (DRE) result [3].

As an organ-specific and not a carcinoma-specific marker, serum PSA may be elevated due to a number of factors such as hyperplastic growth of prostatic tissues, inflammation, prostatic manipulation, urinary retention, sexual activity, and, hypothetically, the presence of undetectable clinically insignificant foci of cancer [4]. In addition, more ''leaky'' prostates with regard to PSA have been postulated for older men. In response to the lack of sensitivity and specificity, several approaches were tested by their capability to distinguish between benign and malignant prostate. Of these, the concepts of PSA velocity and PSA density, the latter being intricately interwoven with PSA changes related to age, have been extensively studied. One major concept to enhance the discriminatory power of the PSA test is the establishment of age-specific reference ranges instead of a single reference range.

2. Lack of sufficient sensitivity and specificity by using a single reference range from 0 to 4 ng/ml for PSA driven detection of early stage prostate cancer

The ideal threshold value for recommendation of prostate biopsy depends on the tradeoffs between false positive and false negative results. Traditionally, a single demarcation between normal and elevated PSA values, 4.0 ng/ml, has been used as an indication for biopsy among men of all ages. Referring to the findings of an early detection study of 6,630 men, Catalona et al. [5] stated the use of total PSA (tPSA) greater than 4.0 ng/ml as a threshold in conjunction with DRE for recommending prostate biopsy to be little less than optimal for all age groups. At variance with this opinion, more recent data provide evidence of the exclusion of an unacceptably high number of patients with clinically significant organ-confined cancer, when a single reference range is applied indiscriminately. Incidental findings from the Prostate Cancer Prevention Trial (PCPT) study [6] as well as data thereof in combination with data of the National Health and Nutrition Examination Survey 2001–2002 (NHANES 2001–2002) [7] revealed that a large number of prevalent cases of biopsy detectable prostate cancer exists in American men with a ''normal'' PSA value less than 4.0 ng/ml.

The standard reference range of 0.0 to 4.0 ng/ml for PSA does not compensate for age-related volume changes in the prostate primarily due to hyperplastic growth of prostatic tissue. For this reason, it was suggested to use age-specific PSA reference ranges, which were to be more sensitive in younger men and more specific in older men. That is, first, when the threshold of 4.0 ng/ml is lowered for younger men, the improved sensitivity was to result in the early detection of more curable, organ-confined tumors. Second, age-specific PSA reference rages were to improve the specificity of the PSA test by raising the PSA threshold for normal among older men.

3. Defining population-based age-specific reference ranges of PSA

Establishing age-specific ranges for serum PSA in order to define age-adjusted minimum thresholds for performing prostate biopsies was suggested to have the advantage of increasing the sensitivity (the probability of the test being positive when the patient is affected with prostate cancer) of PSA testing in younger men as well as enhancing its specificity (the probability that negative test indicates that the patient does not have prostate cancer) in older men, resulting in the increased detection of curable early stage cancers in the younger male population and decreasing the overdetection and probably overtreatment of clinically insignificant cancers in older men [8].

3.1. Age-specific tPSA ranges in populations consisting predominantly of white men

Oesterling et al. [8] were among the first who set out to establish age-specific normalized serum PSA values. In this community-based study, a set of reference individuals was enrolled that consisted of 471 randomly chosen men aged 40 to 79 years who had a prostatic evaluation including a serum PSA determination, digital rectal examination, and transrectal ultrasonography that provided no evidence of prostate cancer. The main finding was that serum PSA concentration strongly correlated with age ($r = 0.43$; $p < 0.0001$) and prostatic volume ($r = 0.55$; $p < 0.0001$). To define reference ranges, the reference values in the set of reference individuals were condensed per decade (Table 1). Using a regression method, the 95th percentile was determined as the upper limit of normal (reference range).

Following the seminal study of Oesterling et al. [8], the existence of direct correlations between serum PSA level, age, and prostate volume was

Table 1 – Age-specific upper reference limits for serum tPSA (ng/ml) concentration in virtually cancer-free men of mainly Caucasian origin

	n	Age (years by decade)						
		21–30	31–40	40–49	50–59	60–69	70–79	80–89
Oesterling [8]	471			2.5	3.5	4.5	6.5	
Dalkin [9]	728				3.5	5.4	6.3	
Anderson [10]	1,716			1.5	2.5	4.5	7.5	
DeAntoni [11]	70,772			2.3	3.8	5.6	6.9	
Oesterling [12]	422			2.0	3.0	4.5	5.5	
Espana [13]	237			2.9	4.7	7.2	9.0	11.4
Lein [14]	1,160	1.16	1.78	1.75	2.27	3.48	4.26	2.64
Kalish [15]	983				2.84	5.87	9.03	
Wolff [16]	697	0.93	1.10	1.15	2.35	3.55	3.95	
Chautard [17]	1,274	1.07	1.37	1.33	2.07	2.82		
Berger [18]*	10,267			1.94	3.5	6.4	8.8	

* With total PSA levels up to 20 ng/ml.

corroborated by the findings of numerous other research groups studying more or less homogeneous white populations [9–18]. They all recommended age-specific reference ranges for PSA (Table 1), the clinical usefulness of most of which has never been tested.

3.2. *The impact of race on age-specific reference ranges for PSA*

There is great ethnogeographical variation in the prevalence of prostate cancer. Therefore, several investigators have evaluated the influence of race on age-specific PSA reference ranges (Table 2). A nearly unanimous finding is that PSA levels in black men are higher compared to those in white men regardless of age and whether or not the patients studied were affected with prostate cancer [11,20,21]. Morgan et al. [20] reported that serum PSA concentrations directly correlated with advancing age ($r = 0.40$); $p < 0.001$) in a large study population of African-American men. Furthermore, they established age-specific PSA reference ranges for this population by elevating the cutoff for prostate biopsy in men older than 50 years compared to white men of the same age group. On the other hand, a lower serum PSA threshold than in white men for recommending prostate biopsy was advocated for African-American men aged 40 to 50 years. Moreover, Moul et al. [21] suggested that higher PSA values in African-American than white Americans with newly diagnosed prostate cancer are due to larger tumor volumes within clinical (TNM) stage categories. Furthermore, reviewing modalities for screening for prostate cancer in African Americans, Moul [22] stressed his view that testing starting at age 40 is recommended using an upper limit of normal for PSA at 2.0 to 2.5 for men between 40 and 49 years of age and that maintaining this lower PSA threshold in older black men is reasonable to optimize the detection of curable prostate cancer. At variance with most other investigators Martin et al. [23] produced data suggesting that no significant difference exists between cPSA or tPSA levels in African-American and white men without prostate cancer in the population of

Table 2 – Age-specific upper reference limits for serum tPSA (ng/ml) concentration in cancer-free Afro-American, Asian, and Hispanic men

	n	Race/Nationality	Age (years by decade)						
			21–30	31–40	40–49	50–59	60–69	70–79	80–89
Morgan [20]	900	African-American			2.4	6.5	11.3	12.5	
DeAntoni [11]	4,485				2.7	4.4	6.7	7.7	
Oesterling [24]	286	Japanese			2.0	3.0	4.4	5.0	
Imai [25]	2,823				2.1	2.9	4.0	5.2	5.9
DeAntoni [11]	900				2.0	4.5	5.5	6.8	
Wang [26]	1,096	Chinese	1.20	1.21	1.23	2.35	3.20	3.39†	
DeAntoni [11]	1,543	Hispanic			2.1	4.3	6.0	6.6	

† ≥70 years.

Table 3 – Age-specific upper reference limits for serum cPSA and fPSA (ng/ml) concentration as well as %fPSA in cancer-free men

	n	Molecular form	Age (years by decade)					
			31–40	40–49	50–59	60–69	70–79	80–89
Oesterling [12]	422	cPSA		1.0	1.5	2.0	3.0	
Espana [13]	755			1.8	2.3	5.9	6.4	
Berger [18]*	10,267			1.66	3.18	5.71	7.22	
Oesterling [12]	422	fPSA		0.5	0.7	1.0	1.2	
Kalish [15]	983				0.61	1.33	1.75	
Oesterling [12]‡	422	%fPSA				15.0		
Lein [14]‡	1,160				12.6			
Kalish [15]‡	983				13.2			
Berger [18]†	10,267			35.9	36.0	38.6	45.3	

* With total PSA levels up to 20 ng/ml.
‡ 5th percentile.
† 95th percentile.

southern Louisiana. These authors speculated that genetic and epigenetic factors distinct to this region may account for this observation.

The prevalence of prostate cancer is conspicuously low in Asian populations. With this in mind, Oesterling et al. [24] wondered whether this apparent racial trait was reflected in low age-specific PSA reference ranges for Japanese men living in their home country. Actually, they observed an increase of PSA with age ($r = 0.33$, $p < 0.001$) and defined age-specific reference ranges for PSA that were lower in Japanese men as compared to white men living in the United States. In a larger study population, these findings were substantiated by Imai et al. [25]. Even lower serum PSA levels than in Japanese men have been reported both in Chinese [26] and Arab men [27], which might be related to the very low incidence of clinical prostate cancer in both populations [27]. In contrast, DeAntoni et al. [11] studying age-dependent reference ranges for PSA in a population of Oriental/Asian origin living in the USA did not find substantial differences in comparison with white Americans.

3.3. *Age-specific reference ranges for molecular forms of PSA*

In blood serum, tPSA represents the fractions of free PSA (fPSA) and PSA complexed to α1-antichymymotrypsin as well as, to a lesser extent, other endogenous protease inhibitors (cPSA). Determinations of fPSA and cPSA roughly add up to the full 100% tPSA. Only a small fraction of PSA bound to α2-macroglobulin is not detectable with an available cPSA assay. Substantial evidence has accrued, demonstrating that the information contained in serum cPSA levels is superior to that in serum tPSA levels resulting in less frequent counselling for prostate biopsies [28,29].

In the same way as for tPSA, age-specific reference ranges for cPSA and fPSA have been evaluated (Table 3). Oesterling et al. [12] and Espana et al. [13] reported that serum concentrations of both cPSA and tPSA correlated directly with patient age (Oesterling: $r = 0.43$ and $r = 0.45$ respectively; Espana: $r = 0.379$ and $r = 0.424$, respectively). In addition, several workers found fPSA to correlate directly with age [12,13,18]. Furthermore, the serum concentration of each molecular form increased by approximately 3% per year with advancing age. Thus, for all 3 ratios, f/tPSA, c/tPSA, and f/cPSA, there was no correlation with patient age. According to the results of Oesterling et al. [12], Lein et al. [12] and Kalish et al. [15] %fPSA is independent of age, whereas Berger et al. [18] found that %fPSA showed significant increasse with age ($p < 0.0001$), which, they argued, may be attributable to the increase in prostate volume with advancing age (Table 3).

3.4. *Major items affecting interstudy comparability*

Tables 1–3 reveal considerable variance of age-specific PSA reference ranges within all age groups. Diverging estimates of PSA cutoffs as a function of age are mainly due to interassay variability, inconsistent calculations of age-specific reference ranges, and verification bias.

Since the advent of PSA testing there have been discrepancies in the results of different assays on the same patient sample. This shortcoming affects the predictive value of PSA in detecting clinically relevant organ confined prostate carcinoma. More-

over, interassay variability hampers direct comparison of findings between studies. Therefore, as outlined by Semjonow et al. [30], the diagnostic application of PSA presupposes an interpretation of the PSA levels based on knowledge of the assay method and the related reference range. Though the differences among PSA assays appear to have decreased since introduction of the WHO 96/670 reference preparation, Interchangeability of tPSA, fPSA and %fPSA values obtained by commercial PSA assays remains inadequate [31,32]. Overall, the results for fPSA from different assays are more diverse than those for tPSA resulting in even more pronounced intermethod differences in the f/tPSA ratio [31].

There are different approaches for estimating PSA reference limits as function of age producing more or less differing results. According to the International Federation of Clinical Chemistry (IFCC) recommendations reference values are defined as the central interval which includes 95% of the statistical distribution of results observed in a reference sample randomly selected from a reference population of reference individuals. As for PSA, however, a one-sided interpretation is appropriate. Therefore, the central 95% interval bounded by the 2.5th and 97.5th centiles is replaced by the lower 95% interval from indetectable to the 95th centile. Centile estimates according to IFCC guidelines do not treat age as a continuous covariate. Instead, the data are mostly subgrouped by decades, thus reducing age-related analysis to a series of computationally simpler decade-by-decade analyses. The studies cited in this review have used either parametric or nonparametric approaches to establish age-specific reference intervals. In the simple parametric approach mean and standard deviation of the data are modeled either directly or after log-transformation. The latter method yields results that allow for the skewed distributional form of the PSA values. Nonparametric methods mostly make no assumptions about the underlying distributional form of the data, thus avoiding the need for transformations. Nonuniform calculatory methods such as regression models or analysis of receiver operating charachteristic (ROC) curves further added to limitations in interstudy comparability.

Reference values for PSA have to be obtained from healthy prostate cancer-free men. Prostate biopsy is considered the gold standard for excluding prostate cancer. Hence, minimizing verification bias would require all reference individuals to consent to having a biopsy – a lesson learned from the PCPT trial [6].

4. Diagnostic impact of age-adjusted PSA thresholds for performing prostate biopsies

Provided that actual age-specific reference ranges for PSA in a homogeneous, absolutely cancer-free population were established, their use in practice as cutoffs for screening a similar population would guarantee 95% specificity. Thus, only a fixed 5% of the men tested in a given age group would be confronted with a false positive result. On the other hand, because of increasing variability of PSA levels in successively older age groups sensitivity might drop to critically low levels. In such a precarious situation, rigorous studies were imperative to determine whether, in fact, this tradeoff was beneficial for older men, especially by weighting the clinical significance of those cancers that would have been missed by using age-specific reference ranges.

Catalona et al. [33] were the first who tested the hypothetic benefit of age-specific reference ranges for PSA with the data of a large multicenter clinical trial. Decreasing the PSA threshold from 4.0 to 3.5 ng/ml in men 50 to 59 years old with normal DRE findings would have resulted in a 45% increase in the number of biopsies (39 of 87) and a projected 15% increase in cancer detection. On the other hand, increasing the PSA cutoff to 6.5 ng/ml in men 70 years old or older would have resulted in 44% fewer biopsies (70 of 159) while missing 47% of organ-confined cancer (7 of 15).

In 1995 a series of studies [34–38] further addressed the evaluation of age-specific PSA reference ranges for early detection of prostate cancer by applying the age-specific ranges suggested by Oesterling et al. [8]. The data of el-Galley et al. [34] supported the use of age-specific reference ranges for PSA in the early detection of prostate cancer. Raised cutoff values, they argued, would be most valuable for patients over the age of 70 years of whom 22% would be spared biopsy. Speights et al. [35] were the first to analyze data from autopsy specimens, and, thus, eliminated some of the limitations adherent to screening studies. They found the use of age-specific reference ranges helpful in increasing the specificity of PSA by eliminating some elevated values in patients above 60 years of age. Oesterling et al. [36] presented data of nearly 3,000 men 60 years or older. They recommended the use of age-specific reference ranges especially for ''the physician who considers it unnecessary to detect small cancers of favorable pathological status in older men who can be monitored safely with annual evaluation''. In contrast with former research groups, Bangma et al. [37]

were reluctant to accept a raising of the PSA threshold for normal. They found the high percentage of missed tumors inadequate for screening prostate cancer.

In an Austrian screening project including 21,078 participants aged 45 to 75 years, Reissigl et al. [38] found an 8% increase in the number of positive biopsies (66 of 778) and organ confined cancers detected in men younger than 60 years of age with a nonsuspicious DRE result by applying the age-adjusted cutoffs. Moreover, using the age-adjusted cutoff points in men 60 years of age or older resulted in 21% fewer biopsies (205 of 983) while missing 4% of organ-confined tomors. Arguing that the detection rate of clinically important organ-confined cancers increases significantly in young men, whereas missing of life-threatening cancers in the older men amounts to only a small number of cases, Reissigl et al. advocated the use of age-specific reference ranges of PSA. To the best of our knowledge, this is the only prospective study in which men with elevated PSA according to age-specific reference ranges were actually invited to undergo further urologic evaluation including ultrasound-guided biopsies.

More recent studies [39–44] produced conflicting results. Weighing the risks against the benefits of using age-specific reference ranges for PSA, Gustafsson et al. [39], Crawford et al. [40], and Wolff et al. [41] argued for maintaining a PSA cutoff at 4.0 ng/ml in screening programs. The data of Poteat et al. [42] supported the use of age-specific reference ranges for PSA demonstrating that assay efficiency and specificity improved and sensitivity, although decreased overall, becomes more uniform across age groups.

In 1996 Partin et al. [43] retrospectively evaluated the pathological stage of tumors that would have been detected or missed by PSA driven diagnoses using age-specific reference ranges. To this purpose, they reviewed the medical records for 4,597 men with localized prostate cancer (stage T1c, T2, and T3a) who had undergone radical retropubic prostatectomy between 1984 and 1994. Favorable pathological criteria were defined as organ-confined disease as well as capsular perforation with a Gleason score of less than 7, whereas unfavorable pathological results were defined as capsular perforation with a Gleason score of 7 or more, seminal vesicle invasion as well as lymph node involvement. There were 74 more cancers detected in men younger than 60 years with the use of age-specific reference ranges (0.0 to 2.5 ng/ml and 0.0 to 3.5 ng/ml for men aged 40 to 49 years and 50 to 59 years, respectively), of which 81% had favorable pathological results. Using age-specific reference ranges in men older than 60 years (0.0 to 4,5 ng/ml and 0.0 to 6.5 ng/ml for men aged 60 to 69 years and 70 to 79 years, respectively) less than 3% of cancers missed were nonpalpable, of which 95% had favorable histology. In all, the potential detection of prostate cancer using age-specific PSA reference ranges increased 18% in younger men and decreased 22% in older men. In conclusion, the authors were in favor of the use of age-specific reference ranges for men younger than 60 years of age and reasoned that their use in older men remained controversial.

Veltri et al. [44] evaluated the diagnostic performance of tPSA versus cPSA in various age groups of 3,597 men who underwent a biopsy procedure for either an abnormal DRE or elevated tPSA test result. In this study, emphasis lay on the impact of increasing age on cutoffs for both tPSA and cPSA to sustain a fixed sensitivity to detect cancer. Specificity was slightly better with cPSA compared to tPSA across all age groups at all sensitivity levels. In order to maintain a given sensitivity level for cPSA or tPSA the cutoffs had to be adjusted upward as age increased.

In a multicenter study Catalona et al. [45] compared three methods (age-specific reference ranges of PSA, PSA density, and percent fPSA) for their utility in cancer detection. The study population consisted of 379 men with prostate cancer and 394 men with benign prostatic disease. In men with PSA concentrations between 4.0 and 10.0 ng/ml and a palpably benign prostate gland both age-adjusted PSA cutoffs (3.5, 4.5, and 6.5 ng/ml in men 50 to 59, 60 to 69, and 70 to 79 years of age, respectively) and percent fPSA enhanced markedly the specificity of serum tPSA for cancer detection, yet percent fPSA maintained significantly higher sensitivity. Age-adjusted PSA cutoffs would have missed from 20% to 60% of cancers in men older than 60 years of age. The commonly used PSA density cutoff of 0.15 would have detected no more than 59% of cancers.

Using a mathematical model to estimate adjusted ROC curves of the PSA test, Punglia et al. [46] addressed the issue of verification bias (i.e., when the disease status of the prostate is not determined bioptically in all subjects who are tested as well as when the probability of verification is based on the test result itself, clinical variables, or both). As evidenced by a significant increase in the area under the ROC curve after adjusting for verification bias, the discriminatory power of the PSA test improved markedly. Separate analyses for men younger and older than 60 years of age showed the area under the curve to increase from 0.69 to 0.86 in younger men and from 0.62 to 0.72 in older men. Hence, the PSA

test performed significantly better in men under 60 years of age than in men past their 60th birthday ($p < 0.001$). Intriguingly these findings suggest that lowering the threshold for biopsy from 4.1 to 2.6 ng/ml in men younger than 60 years would double the cancer detection rate from 18% to 36%, whereas specificity would fall only from 98 to 94%. On the other hand, this study was not conceived to find out which PSA thresholds would be optimal for a particular age group. Rather, it was to point out the implications of following current screening recommendations relying on a single fixed cutoff point for all age groups.

In addition to research into lowering the PSA threshold prompting biopsy, Nadler et al. [47] determined how a lower PSA cutoff would perform in men older than 60 years of age. They found that clinical and pathological characteristics of prostate cancers detected in the PSA range between 2.6 and 4.0 ng/ml were similar regardless of patient age. Overall 16.2% of the men with PSA 2.6 to 4.0 ng/ml were diagnosed with prostate cancer.

5. Is PSA in combination with age a prognostic factor?

The premise of adjusting PSA thresholds for patient age was that PSA interpretation was modulated by taking into account the increasing prevalence of both benign growth and incidental, non-life-threatening cancers among successively older cohorts of men. This latter supposition would imply that the serum PSA level conveys some sort of prognostic information. For example, in a way that enables PSA variables to be interpreted in terms of aggressiveness of prostate cancer. Indeed, recent data of Loeb et al. [48] suggest that a baseline PSA value between the age-specific median (0.7 and 0.9 ng/ml for men aged 40 to 49 and 50 to 59 years, respectively) and 2.5 ng/ml was a significant predictor of developing prostate cancer and was associated with a markedly greater PSA velocity. Moreover, a greater baseline PSA level was associated with significantly more adverse pathologic features and biochemical progression.

In the pre-PSA-era, younger age was mostly believed to signify potentially more virulent disease, and, thus, conveys a poorer prognosis [49,50]. To the contrary, there are data coeval with the former study reporting improved survival of younger prostate cancer patients [51]. Later on, other investigators produced increasing evidence that there is no significant correlation between age and survival [52]. Very recent data of Konski et al. [53] demonstrate that men aged 55 or less who present with localized prostate cancer do not appear to have a worse prognosis.

6. Intergrating principles of PSA density and PSA velocity into concepts of age-adjusted cutoffs for PSA

6.1. *Age-adjusted PSA thresholds depending on abnormal digital rectal examination result*

Punglia et al. [46] described estimates of ROC curves for PSA adjusted for verification bias. In addition, they found that men who had an abnormal (enlarged but not suspicious) DRE result were significantly more likely to undergo prostate biopsy compared with men with a normal DRE result after controlling for PSA level, age, race, and family history ($r = 1.547$; $p = 0.0002$). This paradoxical diagnostic strategy prompted Punglia et al. [54] to argue that an abnormally voluminous prostate would indicate the presence of hyperplasia as a cause for a nonspecific rise in serum PSA level rather than being an indicator of prostate cancer. They tested their hypothesis in a screening study on the impact of age, benign prostatic hyperplasia, and cancer on PSA level. From the data of 6,691 men enrolled in this study ROC curve analyses were performed using adjusted ROC curves for men younger than 60 years separating men with abnormal DRE result from men with normal DRE result as well as the corresponding ROC curves for men 60 years or older. These adjusted ROC curves provided estimates of the mean PSA values in men with and without prostate carcinoma separated by DRE results (Table 4). Separating the analyses by DRE result revealed no difference in the overall diagnostic performance, yet sensitivity and specificity at a given cutoff point were different. For each cutoff point sensitivity was higher and specificity lower in the abnormal DRE cohort. This finding would imply that the threshold point for recommending biopsy should be higher among men with an abnormal DRE result, and, in addition, higher among men 60 years or older. The authors' opinion is that the current threshold of 4.0 ng/ml should not be applied indiscriminately.

6.2. *Prediction of the change of serum PSA concentration over time in individual men*

The downside of defining age-specific reference ranges for 'normal' levels of PSA from cross-sectional data is that resultant PSA ranges in the reference intervals are broadly mirroring the

Table 4 – Mean PSA values in men with and without prostate carcinoma separated by DRE result

	DRE	Age < 60 years	Age ≥ 60 years
		Geometric mean PSA (ng/ml)	Geometric mean PSA (ng/ml)
With cancer	Normal	2.05	2.66
	Abnormal*	2.56	3.90
Without cancer	Normal	0.78	1.23
	Abnormal*	0.97	1.75

* Abnormal DRE indicates enlarged prostate size but not suspicious for cancer.
From data of Punglia et al. [54].

population inherent variability of serum PSA levels rather than meeting the change of PSA concentrations to be expected in a given individual. To circumvent this shortcoming, the reference individuals may have to be classified into more homogeneous subgroups. There is less variation in the reference values of men matched by initial PSA and age, e.g. in a subgroup of men whose PSA was 2.0 ng/ml at age 50. Such subgroups can provide reference ranges for 'normal' levels of PSA, against which developing tumors might be identified more easily than against the standard age-specific reference ranges for PSA representing the population average.

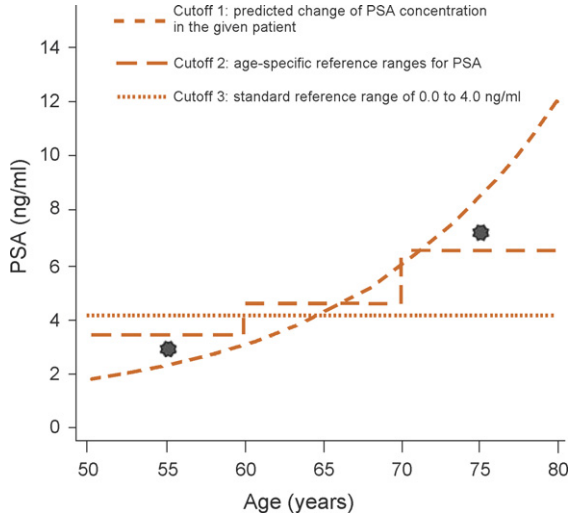

Fig. 1 – Comparison of the impact of three differently derived cutoffs for PSA on the advice of whether or not to undergo biopsy in a man with an initial PSA value of 2.0 ng/ml at age 50: Cutoff 1: predicted change of serum PSA concentration in the given patient [55]), Cutoff 2: age-specific reference ranges according to Oesterling et al. [8]), Cutoff 3: standard reference range of 0.0 to 4.0 ng/ml. If, in this case, the man's PSA had risen to 3.0 ng/ml at age 55 (left asterisk), he would be confronted with the recommendation of biopsy only when applying cutoff 1, whereas his PSA would be still beneath cutoff 2 and 3. On the other hand, a PSA value of 7.0 ng/ml at age 75 (right asterisk) is above the upper limits of both cutoff 2 and cutoff 3, but there would be no advice for biopsy by applying cutoff 1 (adapted from Bosch et al. [55]).

Thus, based on longitudinal data from individual community-based prostate-cancer-free Dutch men aged 50 to 70 years, Bosch et al. [55] created a model, which can be applied to predict normal PSA changes over time for an individual. A bivariate multilevel growth curve model that allows for estimates of the influence of individual characteristics of men on PSA and prostate volume was used to estimate the pattern of change of both PSA and prostate volume with age. The analyses provided evidence of positive correlations between log PSA and log prostate volume as well as the rate of change of log PSA and the rate of change of log prostate volume. In its final form the model showed that PSA was related to age only. Thus, the future PSA of an individual can be predicted based on his age and known history of PSA such as an initial PSA value at age 50. Applying this individualized method would result in more biopsies in men below 65 and fewer biopsies in men aged above 65 as compared to the method using a PSA cutoff of 4.0 ng/ml or age-specific reference ranges (Fig. 1). By implicating the history of PSA, this model integrates the principles of age-specific reference ranges for PSA and PSA velocity. Tests in a separate screening population are required to investigate the ability of the proposed model to make progress in the early identification of progressive/aggressive prostate cancer, or the development of more sensitive or specific screening regimens.

7. Conclusion

Although a majority of studies including the prospective one of Reissigl et al. [34] advocate the use of age-specific reference ranges for PSA, this method did not become widely accepted in clinical use and screening programs. Polascik et al. [56] specifically refer to the fact that age-specific reference ranges neither have ever been officially approved nor have they been recommended by

manufacturers of commercially available PSA assays. Even though this statement was made in 1999 the same holds true in 2006. On the other hand, the situation recently has changed insofar as results from the PCPT trial revealed a high prevalence of prostate cancer in men of all ages with tPSA between 2 and 4.5 ng/ml [6]. As a consequence, clinging to both the standard reference range of 0.0 to 4.0 ng/ml and the concept of age-specific ranges for PSA is increasingly cast into doubt. Wherever possible, physicians should take into account that the dynamics of PSA is different in prostate cancer-free men versus men harboring this tumor.

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CME questions

Please visit www.eu-acme.org/europeanurology to answer these CME questions on-line. The CME credits will then be attributed automatically.

1. The intended aim of using age-specific reference ranges is to:
   A. Minimize the number of prostate biopsies per biopsy.
   B. Improve sensitivity in younger men (<60 years).

C. Improve sensitivity in older men (>60 years).
D. Improve specificity in younger men (<60 years).

2. For example according to Oesterling et al., 1993 the age-specific PSA cut off for a 45 year old man is:
   A. 3.5 ng/ml.
   B. 2.5 ng/ml.
   C. 4.5 ng/ml.
   D. 6.5 ng/ml.

3. Ratio of free to total PSA is used to better discriminate between malignant and benign. There is:
   A. No correlation with patient age.
   B. Approximately an increase of 30% per decade.
   C. A decrease of 30% per decade.
   D. No change for free PSA with patient age.

4. The use of age-specific PSA cut offs in a screening pattern:
   A. Remains controversioal, because an unacceptable number (up to 60%) of clinically significant cancers would be missed in older men (>60 years).
   B. Is not influenced by different assay systems.
   C. Seems to be mandatory, because all studies have been thoroughly screened for prostate cancer.
   D. Is independent from racial differences.

5. Major items affecting interstudy comparability are:
   A. Different PSA-assay methods.
   B. Different approaches for estimating PSA reference limits.
   C. Minimizing verification bias would require all reference individuals undergoing biopsy to exclude cancer.
   D. All answers are correct.

6. The ideal threshold value (cutoff) for recommendation of prostate biopsy depends on the trade-offs between false positive and false negative results. Traditionally, a single demarcation between normal and elevated PSA values, 4.0 ng/ml, has been used as an indication for biopsy among men of all ages. Recently published studies:
   A. Revealed that a large number of prevalent cases of biopsy detectable prostate cancer exists in men with a ''normal'' PSA value less than 4.0 ng/ml.
   B. Recommend a cutoff of 4.0 ng/ml should be further used to minimize overdetection of prostate cancer.
   C. Argue that PSA should not be used in screening patterns.
   D. Recommend PSA-testing from the early thirties in order to increase specificity.