Optimal Baseline Prostate-specific Antigen level to Distinguish the Risk of Prostate Cancer in Healthy Men between 40 and 69 Years of Age

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<Title page>

Optimal Baseline Prostate-specific Antigen level to Distinguish the Risk of Prostate Cancer in Healthy Men between 40 and 69 Years of Age

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This certifies that the Master's Thesis of
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ABSTRACT

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Objectives: To evaluated the optimal baseline PSA level at different ages to determine the risk of CaP.

Patients and Methods: We analyzed a large cohort of 6,651 Korean men in age 40-69, The serum PSA levels for the men were measured at one institute from 2000 to 2004 and were determined to be between 0-4 ng/ml. Patients were divided into 4 groups of 25th-percentile intervals, based on initial PSA level. Of these, the group which has a increased risk were selected, and the optimal value was determined by the maximal AUC from the receiver-operating characteristic curve (ROC) within the selected group. The risk of CaP diagnosis was evaluated by Cox regression.

Results: The mean follow-up period was 8.3 years. The optimal PSA values to distinguish the risk of CaP were 2.0ng/ml for 50- to 59-year-olds and 1.5ng/ml for 60- to 69-year-olds. Patients with a baseline PSA level greater than the optimal value had a 33.15 and 24.41-fold increase in the age-adjusted prostate cancer risk, respectively.

Conclusions: Baseline measurements of PSA should begin at the age of 50. Furthermore, the optimal cutoff values depend on the age.

Impact: Optimal PSA cutoff value to distinguish the risk of prostate cancer was different depending on the incidence of prostate cancer of ages.

Key words : Prostate-specific Antigen, Screening, Prostate Neoplasm, Asian Continental Ancestry Group

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I. INTRODUCTION

The American Urological Association (AUA) and American Cancer Society (ACS) recommend that prostate cancer screening begin at 50 years of age for men with an average risk of prostate cancer (CaP) and even earlier for men with a higher risk for prostate cancer due to risk factors, such as a positive family history in a first-degree relative or an African American heritage. Prostate cancer screening is performed for the early detection of curable prostate cancer. Prostate cancer deaths are seen in men as young as 35 to 44 years of age, according to Surveillance, Epidemiology, and End Results (SEER) data. These deaths indicate that men younger than the recommended screening age of the AUA and ACS for the early detection of prostate cancer can also be affected by the disease. Therefore, depending on the risk for developing prostate cancer, the prevention and detection strategy should be adjusted to include younger men. To assess the risk of prostate cancer, baseline prostate-specific antigen (PSA) levels are used. In 2005, Whittemore

and colleagues[1] reported that PSA levels in young adults were useful predictors of CaP detection. Loeb et al.[2], reported that the baseline PSA levels for men in their 40s were a stronger predictor of CaP risk than ethnicity, family history, or digital rectal examination findings. Ultimately, the NCCN (National Comprehensive Cancer Network) recommended a baseline PSA test for all men, starting at 40 years of age, in order to assess the risk for CaP. It has been determined that PSA level distributions differ based on ethnicity and age [3-5]. Therefore, research should be conducted taking into account ethnic differences.

Based on healthy-screened Korean men with PSA levels between 0-4 ng/ml, we assessed the optimal baseline PSA levels for the prediction of the risk of developing prostate cancer in Korean men.

II. MATERIALS AND METHODS

1. Study Population

This study was approved by our institutional review board. Between January 2000 and July 2004, a total of 6,651 men between the ages of 40 and 69, with baseline PSA levels between 0-4 ng/ml during routine health check ups, were enrolled in the study. Patients who had a previous diagnosis of CaP, a history of prostate surgery, or who had received 5-alpha reductase inhibitors within three months were excluded from the study. In July 2009, cases of CaP in enrolled patients were identified using data available from the Korean National Health Insurance Corporation (NHIC) website, which links to the Korean Severe Patient Registry. This registry includes data for over 99% of all cancer cases diagnosed in Korea[6]. Of our total study sample of 6,651 men, 17 died due to diseases other than prostate cancer during the study period.

2. Assessment of risk

Patients were divided into 4 groups at 25th percentile intervals based on initial PSA. Of these, the group which has a increased risk was selected and the optimal PSA value was determined using the maximal area under curve (AUC) by receiver-operating characteristic curve (ROC) within the selected group. The risk of developing prostate cancer in the enrolled men was studied based on the optimal PSA value. 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 baseline PSA level for determining risk.

3. PSA testing

Serum PSA levels were measured using an Elecsys 170 assay (Roche Diagnostics, Mannheim, Germany). Vacutainer tubes were used (Becton Dickinson, Oxford, UK) for blood collection, and the specimen was centrifuged after venipuncture and collection. After centrifugation, the specimens were immediately frozen at -70°C and were assessed for PSA within three days.

4. Statistical analysis

All statistical tests were two-sided. A p-value < 0.05 was considered to be statistically significant (SAS software, version 9.1). A Kaplan-Meier survival analysis was performed to estimate prostate cancer-free probability, with time considered as a function of the baseline PSA level. Subjects without cancer were censored at death or in July 2009. A log-rank statistical test was used to compare the Kaplan-Meier survival curves among the PSA groups.

A Cox proportional hazards regression model was used to examine the long-term relationship between baseline PSA level and prostate cancer risk. Comparison of the performance of each Cox model was calculated by C statistic (area under the ROC curve). The Hazard ratio (HR) and 95% confidence intervals were estimated using the Cox regression model, with a PSA level lower than the cutoff value treated as the reference group.

III. RESULTS

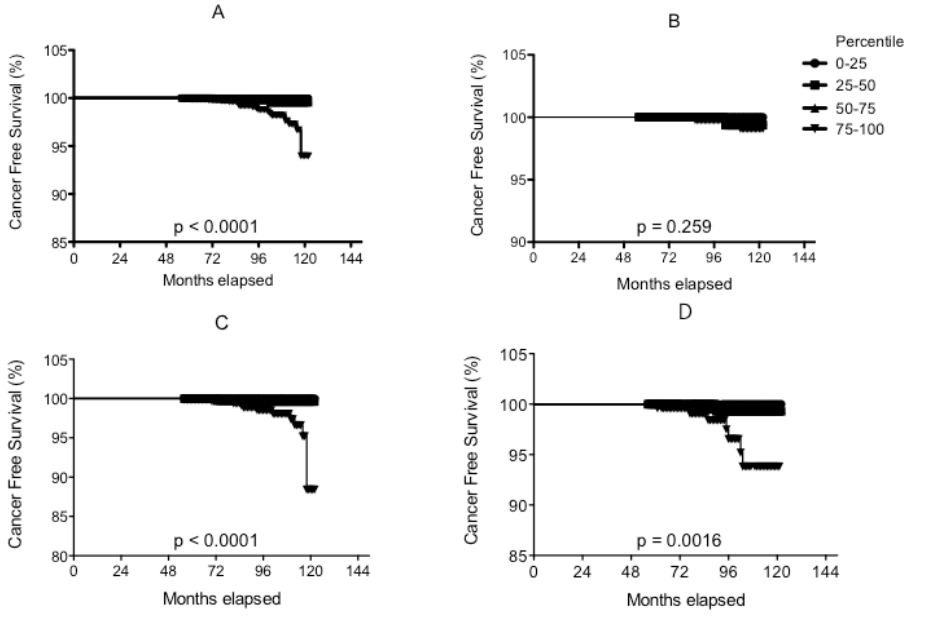
At baseline, the patients had a mean age of 50 years and a mean PSA value of 0.83 ng/ml. The median PSA levels were 0.72, 0.81, and 0.93 ng/ml, and the third quartile PSA levels were 1.08, 1.23, and 1.51 ng/ml for men in their 40s, 50's, and 60's, respectively. The mean follow-up period was 8.3 years. Prostate cancer was detected in 27 of the 6,651 subjects. After initial PSA measurement, prostate cancer was discovered after at least 2.2 years in men in their 50's and 2.7 years in men in their 60's (Table 1).

Table 1. Characteristics of baseline PSA study cohorts.

Age (years)	Baseline PSA Level (ng/ml)	No. of Men	No. of Cancer Cases	Cancer Detection Rate	Mean Follow Up year to Detect Prostate Cancer (range)
40-49 (n=3417)	0.00-0.49	619	0	0.0%	
	0.50-0.99	1677	1	0.1%	8.5
	1.00-1.49	726	1	0.1%	9.4
	1.50-1.99	227	0	0.0%	
	2.00-2.49	93	1	1.1%	7.2
	2.50-2.99	45	0	0.0%	
	3.00-3.49	15	0	0.0%	
	3.50-3.99	15	0	0.0%	
	Mean			0.1%	8.7 (9.2-9.4)
50-59 (n=2234)	0.00-0.49	408	0	0.0%	
	0.50-0.99	1013	2	0.2%	5.9 (5.9-6.0)
	1.00-1.49	474	1	0.2%	8.6
	1.50-1.99	174	1	0.6%	6.2
	2.00-2.49	88	3	3.4%	6.5 (4.7-8.3)
	2.50-2.99	41	2	4.9%	6.5 (6.3-6.6)
	3.00-3.49	21	3	14.3%	5.2 (2.2-8.4)
	3.50-3.99	15	3	20.0%	4.8 (2.9-7.3)
	Mean			0.7%	6.3 (2.2-8.6)
60-69 (n=1009)	0.00-0.49	143	0	0.0%	
	0.50-0.99	394	1	0.3%	7.5
	1.00-1.49	207	0	0.0%	
	1.50-1.99	110	2	1.8%	5.7 (2.9-8.3)
	2.00-2.49	73	1	1.4%	8.4
	2.50-2.99	37	3	8.1%	4.4 (3.6-5.3)
	3.00-3.49	18	0	0.0%	
	3.50-3.99	18	2	11.1%	4.7 (2.7-6.7)
	Mean			0.9%	6.2 (2.7-8.4)

When all subjects were classified into 4 groups based on 25th percentile intervals of baseline PSA level, the risk of prostate cancer was significantly increased in men with a baseline PSA level of more than the 75th percentile. However, men in their 40s did not have a significantly increased risk of prostate cancer (Figure 1).

Figure 1. Cumulative prostate cancer-free survival according to the age and baseline PSA percentile

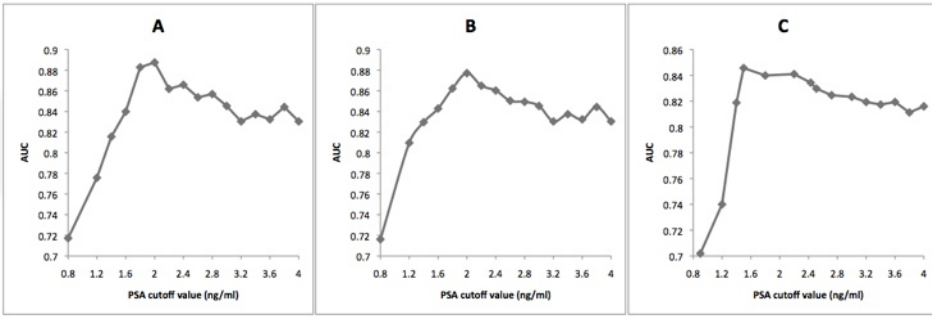


Survival curves for men aged (A) 40 to 69.9 years, (B) 40 to 49.9 years, (C) 50 to 59.9 years and (D) 60 to 69.9 years. Markers represent prostate cancer and sensored cases. With time, prostate cancer incidence increased significantly in men with a baseline PSA more than the 75th percentile (reverse triangle), except for men in their 40s (log-rank test for trend)

Above the 75th percentile of the baseline PSA level, the cut-off values with the

greatest sensitivity and specificity were 2.0ng/ml (93 percentile) for men in their 50's and 1.5ng/ml (75 percentile) for men in their 60's (Figure 2).

Figure 2. Trend of area under curve according to a baseline PSA cut-off value greater than the median PSA level.



AUC: area under curve, PSA: prostate-specific antigen, A: group of 50- to 69-year-olds, B: 50- to 59-year-olds, C: 60- to 69-year-olds.

As compared with the group with a baseline PSA level less than the cut-off value, the group with a PSA level higher than the cut-off value had a 33.15-fold increased risk for diagnosis of CaP in their 50's ($p < 0.0001$) and 24.41-fold increased risk in their 60's ($p = 0.03$). The age-adjusted CaP hazard ratio was also significantly increased 30.8-fold for men in their 50's and 24.1-fold for men in their 60's.

However, when the cut-off value was set at the median baseline PSA, the risk of CaP was 14.2-fold increased for men in their 50's ($p = 0.01$) and 8.3-fold higher for men in their 60's ($p = 0.04$) (Table 2).

Table 2. A comparison of risk of developing prostate cancer in Korean men with baseline PSA values by age.

Age (years)	PSA cutoff level (ng/ml)	HR† (95% CI)	P
50-59	0.81*	14.22 (1.73-100.61)	0.01
	1.2‡	20.46 (4.41-87.03)	<0.0001
	2	33.15 (9.76-97.97)	<0.0001
	2.5	28.22 (9.00-71.78)	<0.0001
	3	27.45 (8,67-68.87)	<0.0001
60-69	0.93*	8.30 (1.01-65.87)	0.04
	1.5‡	24.41 (3.03-196.58)	0.03
	2	22.27 (2.85-185.14)	0.002
	2.5	18.13 (4.80-68.48)	<0.0001
	3.5	9.99 (2.44-40.25))	0.001

PSA: prostate-specific antigen, HR: hazard ratio, CI: confidence interval

* : median baseline PSA value, ‡ : 75th percentile of baseline PSA value

† :HR estimated by Cox regression model for comparisons with the reference group (lower than cut-off).

IV. DISCUSSION

Based on our results, the median baseline PSA levels were 0.72 ng/ml, 0.81 ng/ml, and 0.93 ng/ml for men in their 40s, 50's, and 60's, respectively. These results are similar to those of previous studies [3,4]. To estimate the risk of prostate cancer, the use of the baseline PSA level is useful[7]. Therefore, we evaluated the risk according to the baseline PSA. In men over the age of 50, the group with a baseline PSA higher than the 75th percentile had a significantly different risk, as compared to their age-specific lowest quartile baseline PSA level (Figure 1A). PSA level is also used as a screening tool to detect prostate cancer. Most diagnostic tools have cut-off points for maximal specificity and sensitivity. Therefore, it was important to determine the PSA value with the maximal AUC according to the receiver-operating characteristic curve.

When the data were evaluated for men in their 50's, and, with regard to the median baseline PSA, there was not sufficient area under curve to provide a cut-off value. At this point, the AUC was approximately 0.7.

Ultimately, the optimal baseline cut-off PSA values for determining the risk of prostate cancer were 2.0ng/ml and 1.5ng/ml for men in their 50's and 60's, respectively. The cut-off value for men in their 50's was lower than that for men in their 60's. This difference is likely due to the lower rate of developing CaP in younger men in this study. If the overall incidence of CaP increases, the age-specific cut-off value of baseline PSA may decrease, as has been observed in statistic results based on Western populations[8].

Upon reviewing the results of similar studies, we found that several authors reported that the median baseline PSA was used as a cut-off value for risk stratification in Western populations. They reported a dozen-fold increased risk of CaP diagnosis [9,10]. However, the authors did not evaluate the lowest and highest quartile value of

baseline PSA. Therefore, it is unknown which quartile had the greater affect.

Tang et al. recently reported a 1.5 ng/ml cut-off value for estimating the risk of developing prostate cancer, which was not the median PSA value[11]. However, the authors adjusted their subjects by age, but did not stratify by age, as we did in our results. If the study had examined the subjects divided by age decade, the results might have been different because the PSA level used to estimate prostate cancer in younger ages is quite different from that used in older ages. And progression rates also differ with ages. Especially in Koreans, the PSA progression curve rapidly increases, starting at age 50, unlike the steady progression pattern in patients aged 40 or younger[3].

Wright et al.[12] also reported that the baseline PSA levels reflect the long-term risk of prostate enlargement. But the cohort size of that study was too small to produce a meaningful cutoff level.

Unlike other studies, our study did not reveal a significant difference in the risk of prostate cancer among the 4 quartile groups at ages 40s. This is probably because of the low incidence of prostate cancer in Korean men.

According to the Surveillance, Epidemiology, and End Results data, CaP deaths occur in North American men between the ages of 35 and 44[13]. Similarly, CaP deaths are also beginning to occur in Korean men younger than 50, and there is an increasing trend toward even younger men dying from CaP[14]. The age-adjusted incidence rate is 159.3 per 100,000 men per year in the US population,[13] as opposed to 12.7 in the Korean population[15]. This ethnicity-based difference may be attributed to two factors discussed below. First, a relatively low overall CaP incidence rate in Korean men may lead to a low incidence at age 40 because prostate cancer requires time to manifest. Therefore, if the overall incidence is reduced, prostate cancer occurrences may be

reduced in younger age groups. Second, Korean men ultimately may not have a risk of CaP because of a lack of gene for familial prostate cancer and/or lack of African heritage, as compared to individuals in Western populations[16], both of which are factors associated with the development of prostate cancer at earlier ages. Based on these results, baseline PSA testing beginning at age 40 is not yet an effective screening strategy for Korean men. We suggest that baseline screening should begin at age 50 for Korean men. Furthermore, we recommend that the screening strategy utilizes different baseline PSA levels for cut-off values in men in their 50's and 60's.

There were some limitations to this study. First, subjects of the study were participants of a routine health check-up. Therefore, these results might not be the same as those seen in the normal population. Second, digital rectal examination (DRE) was not included in the screening procedure. When PSA values are low, a positive DRE result is associated with CaP in only 3% to 5% of the cases [17,18]. Vis et al. 19 calculated that one would have to perform 289 DREs to find one case of clinically significant CaP in patients with a PSA level less than 3.0 ng/ml. Therefore, we assumed that the omission of DRE did not greatly affect our results.

Third, the presence of CaP was not confirmed by a pathologic report based on prostate biopsy, but rather from data from a cancer registry maintained by NHIC. Therefore, we were unable to access complete pathologic information for all cohort members.

V. CONCLUSION

Baseline PSA values are useful tools for determining the risk of developing prostate cancer in Korean men between the ages of 50 and 60. Appropriate follow-up strategies should be determined not only according to optimal baseline PSA level, but also according to patient age. We recommend that men between the ages of 50 and 60 should have their baseline PSA levels measured, and they should visit their physician according to their risk category.

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ABSTRACT(IN KOREAN)

70세 이하의 한국 남성의 전립선 암 발생 예측에 쓰이는 기초 전립선 특이항원(baselinePSA)의 효용성 및 적정 절단치

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박 경 기

최근 연구에서는 처음 측정한 전립선 특이 항원(baseline PSA)수치가 미래의 전립선 암의 발생을 예측하는데 중요한 요인으로 밝혀졌다. 2009년 AUA guideline에 의하면 각 연령군의 중위값을 기준으로 초과된 환자군이 이내의 환자군에 비해 전립선 암 발생률이 높기 때문에 좀더 빈번한 PSA 검사를 하도록 하고 있다. 각 연령별 PSA 중위값은 인종별로 차이가 있는데 한국 남자에서는 중위값을 기준으로 전립선 암 발생률의 차이가 있는지 알아보고자 한다. 2000 년 부터 2004년까지 본원 건강검진센터에서 검진을 시행한 6651명의 남

자를 후향적으로 분석하였다. 연령은 40세이상 69세 이하로 제한하였고 본원에 첫 내원하여 시행한 전립선 특이 항원(baseline PSA)이 0-4사이인 남자를 포함하였다. 40-69세까지의 남자를 10년씩 나누어 3군으로 나누고, 환자를 PSA에 따라서 4분위수로 나뉘었다. 그리고 각 군에서 위험도가 증가하는 군을 골라서 AUC를 계산하였다. 평균나이 50세, 평균 PSA 0.96ng/ml, 평균 추적기간 8년 2개월이었다. 각 연령별 PSA중앙값은 40대와 50대가 각각 0.79와 0.81ng/ml, 60대가 0.93ng/ml이었다. 기초 PSA 값이 중앙값 이상인군에서 0.60%의 환자가 평균 6년4개월 후 전립선암이 진단되었고, 그렇지 않은 군에서 0.03%의 환자가 진단되었다.(OR=18.52, 95%CI:2.5-140.8, p=0.004). 연령별 PSA절단치를 기준으로 높은 군이 낮은 군에 비해서 전립선암 발생 위험도가 33.15배, 24.41배로 50대와 60대에서 각각 나타났다. baselinePSA의 측정은 50대에서 부터 시작하는 것이 좋겠다. 그리고 연령별 절단치에 맞추어서 개개인의 추적 관찰을 달리하여야 하겠다.

핵심되는 말 : 전립선 특이 항원, 검진, 전립선암, 아시아인