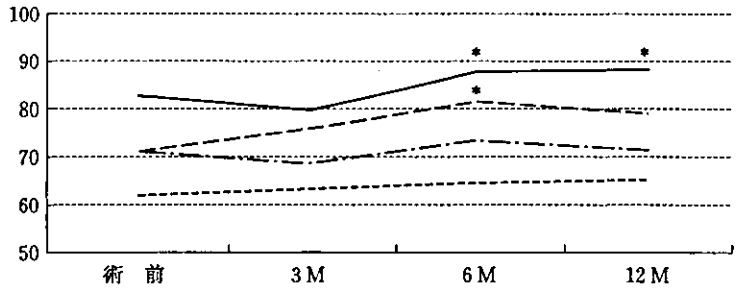

図3 前立腺全摘術後の一般健康関連QOLの推移
mental health や social function は術前よりも良くなっている.

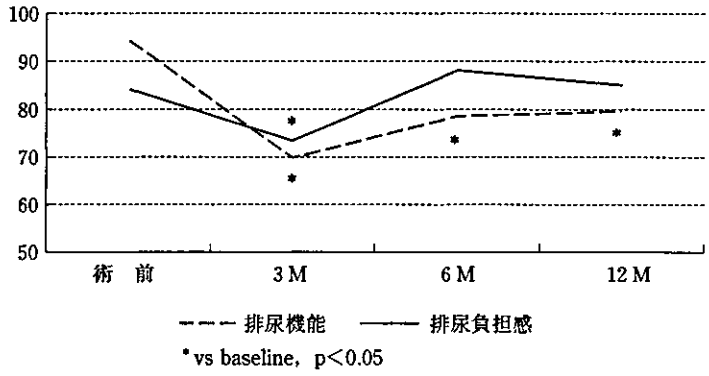

図4 前立腺全摘術後の排尿機能と排尿負担感
UCLA Prostate Cancer Index による調査で, スコアが高いほどQOLが良いことを示す.

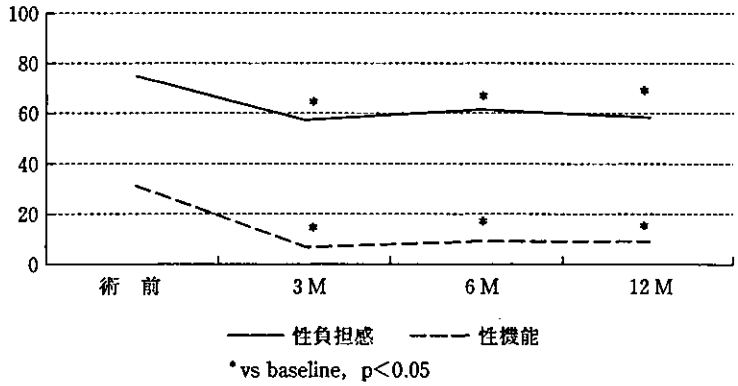

図5 前立腺全摘術後の性機能と性負担感
UCLA Prostate Cancer Index による調査で, スコアが高いほどQOLが良いことを示す.

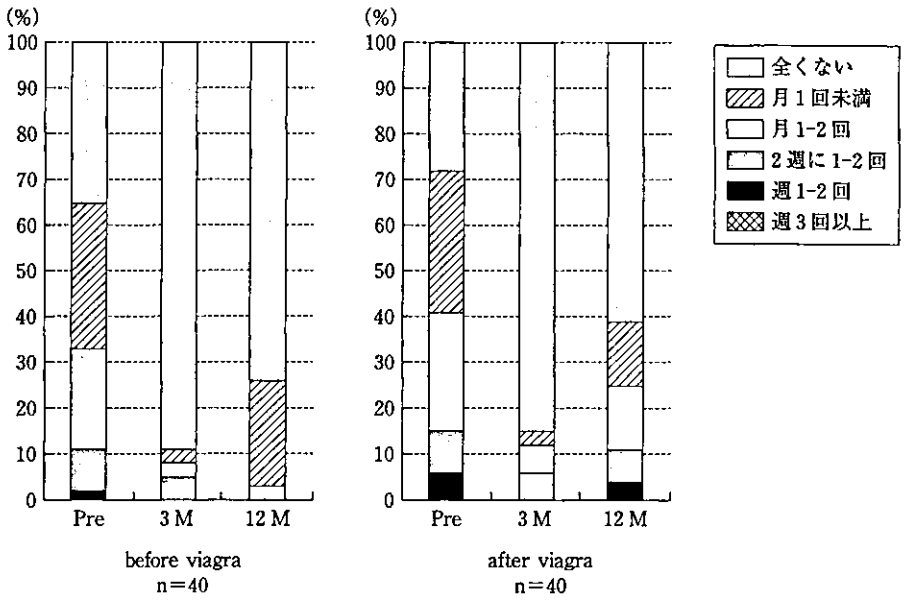

図6 前立腺全摘術後の性的活動に関する縦断調査
バイアグラ®発売以降に術後の性的活動が改善していることが伺える.

7. QOL改善のための新たな試み

神経温存術式により性機能の一定の回復がみられるが，一方で十分な勃起機能の回復が得られない症例を多く経験する．著者らの調査でも神経温存群では12カ月の時点で非温存群より有意な性機能の改善がみられたが，その改善程度は術前の性機能に比べて極めて不十分なものであった．特に片側神経温存例の性機能回復が不良である．一方，神経温存がなされていればクエン酸シルデナフィル(バイアグラ®)の治療効果が期待できる[6]．なかでも両側神経温存例では70%以上の有効率が確認されている．また著者らが行ってきた縦断的調査でも，バイアグラ®処方が可能になった1999年以降でsexual activityが大きく改善されていることが伺える(図6)．

このような背景の中，勃起神経の再建術が試みられている．腓腹神経あるいは陰部大腿神経を採取し，片側，あるいは両側の陰茎海綿体神経の遠位端と近位端との間に採取した神経を移植する(図7)．Kimらは手術後5カ月から勃起が出現する症例が現れ始め18カ月後に最大の勃起機能の改善が認められ，両側で神経移植を行った症例の75%で勃起機能が回復すると報告しており，両側の神経温存がなされた症例とほぼ同等と考えられている[7]．著者らも2000年から神経再建術を開始し，現在までに30例以上に行ってきた．その結果，片側神経温存のみの場合に比べ，神経移植例では明らかに術後勃起機能の回復が良好であった．神経移植の効果判定には少なくとも1年以上の観察が必要であり，今後の長期的成績が期待される．

おわりに

限局性前立腺癌に対する外科療法について，著者らの成績を中心に最近の話題も含めて概説した．Walshの解剖学的前立腺全摘術が開発されてから既に20年以上が経過した．現在でも手術法は進化しており，更なる成績向上の努力が続いている．一方，早期前立腺癌の治療オプションは多様化しており，それぞれのアウトカムについての客観的で科学的な手法に基づいた研究が急がれる．

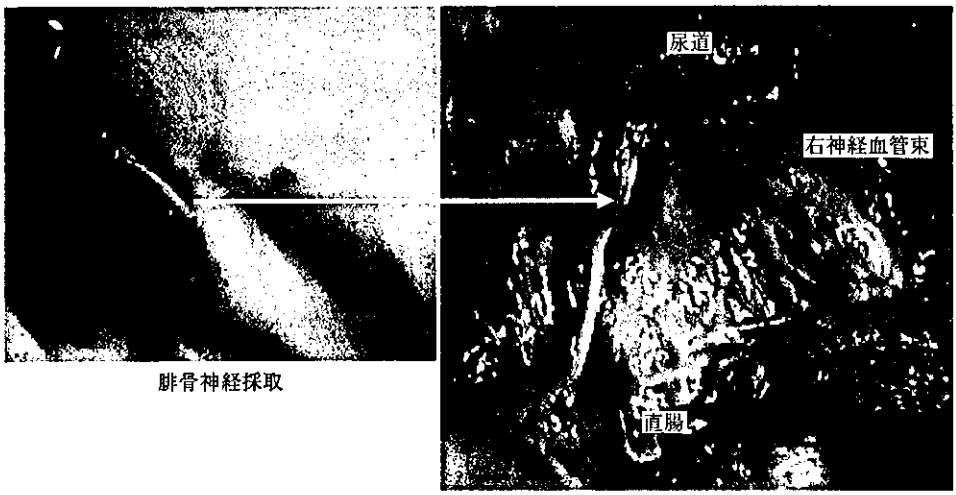

図7 前立腺全摘術における陰茎海綿体神経再建術

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Prostate Carcinoma Detection and Increased Prostate-Specific Antigen Levels after 4 Years in Dutch and Japanese Males Who Had No Evidence of Disease at Initial Screening

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BACKGROUND. In the current study, the authors set out to investigate the possibility that increased prostate-specific antigen (PSA) levels in Dutch and Japanese men without suspicious findings at initial prostate cancer screening were indicative of the risk of newly developing clinical malignancy in the Netherlands and Japan.

METHODS. Between 1992 and 2000, 2650 men ages 55–74 years who had PSA levels < 4.0 ng/mL and no suspicious findings on digital rectal examination were entered into the current study from a population-based prostate cancer screening cohort in Gunma Prefecture, Japan. In addition, between 1994 and 1997, 3163 men with the same clinical background were entered into the current study from the Rotterdam (Netherlands) Section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Prostate carcinoma incidence and the cumulative probability of freedom from PSA increases to levels > 2.0, 3.0, and 4.0 ng/mL, respectively, after 4 years of observation were compared between the Japanese and Dutch populations. The predictive value of initial PSA level, age at study entry, and geographic location also were investigated using Cox proportional hazards models.

RESULTS. The overall risk of developing prostate carcinoma during the 4-year observation period was significantly higher for the ERSPC Rotterdam cohort (5.2%) compared with the Gunma cohort (1.6%). The cumulative probability of freedom from prostate carcinoma detection and freedom from an increase in PSA levels to ≥ 4.0 ng/mL (PSA progression) decreased significantly with increasing initial PSA level and did not differ significantly between Japanese and Dutch patients whose initial PSA levels fell within the same range (0.0–0.9, 1.0–1.9, 2.0–2.9, or 3.0–3.9 ng/mL). Multivariate analysis also revealed that after controlling for age and initial PSA level, the probability of PSA progression was the same for Japanese and Dutch men. Initial PSA level was the only variable found to be significantly predictive of PSA progression on multivariate analysis ($P < 0.0001$).

CONCLUSIONS. The risk of developing prostate carcinoma within a given 4-year period is greater for Dutch males ages 55–69 years compared with their Japanese counterparts, because the former have higher PSA levels. Nonetheless, there appears to be no significant difference in prostate carcinoma risk between Dutch and Japanese males whose baseline PSA levels fall within the same range. *Cancer* **2005; 103:242–50.** © *2004 American Cancer Society.*

KEYWORDS: prostate carcinoma, prostate-specific antigen, screening, PSA progression.

It is widely known that the probability of developing prostate carcinoma is strongly correlated with serum prostate-specific antigen (PSA) levels.[1,2] Thus, if the risk of a future increase in PSA levels is

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known, the future risk of developing prostate carcinoma can also be estimated. Two recent studies have investigated the cumulative risk of PSA increases to levels > 4.0 ng/mL in males with initial PSA levels ≤ 4.0 ng/mL.[3,4] In both American and Japanese males, the cumulative probability of such an increase over 5 years of follow-up was found to grow larger with increasing initial PSA level. These results suggest that baseline PSA level could serve as a useful predictor of future prostate carcinoma risk; however, the two studies that yielded these findings may have included numerous cases in which patients whose baseline PSA levels were within the reflex range of 0.0–3.9 ng/mL had abnormal findings on digital rectal examination (DRE) at initial screening.

Given the information that is currently available, we believe that an evaluation of the proportion of men with baseline PSA levels < 4.0 ng/mL and normal findings on DRE at initial screening who develop detectable prostate carcinoma and experience PSA increases over the subsequent 4-year screening interval is warranted. The results of such an analysis may be strongly correlated with the risk of newly clinically manifested prostate carcinoma in the populations examined.

In the current study, the issue at hand was addressed by investigating patients from two large, population-based screening studies—one based in Europe and the other based in Japan.

MATERIALS AND METHODS

Between January 1992 and December 2000, 11,880 men ages 55–74 years had their serum PSA levels measured as part of a population-based prostate carcinoma screening study conducted in Gunma Prefecture, Japan. All participants received an invitation letter (including a fact sheet on prostate carcinoma screening) from the local government and chose to take part in the study on the basis of the information presented to them. Six thousand one hundred thirty-eight of the 11,880 participants also underwent DRE at initial screening. Of these 6138 men, the 2650 who had serum PSA levels < 4.0 ng/mL and no suspicious findings on DRE and who underwent rescreening at least once within 4 years of baseline were enrolled in the current study. Although annual screening was recommended by the local government, screening practices were left to the patient's discretion. Of the 2650 men who were included in the current study, 1664 (62.8%) also underwent transrectal ultrasonography (TRUS) at initial screening and had no suspicious findings.

Between April 1994 and March 1997, after providing informed consent, 8922 male volunteers ages 55–74 years participated in the Rotterdam (Netherlands) Section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Serum PSA levels were measured for all participants. Six thousand nine hundred eighty-three of the 8922 participants underwent both DRE and TRUS. Of these 6983 men, the 3163 who had PSA levels < 4.0 ng/mL and normal findings on DRE at initial screening and who underwent rescreening within 4 years of baseline were enrolled in the current study. All 3163 participants who were included in the current analysis also underwent TRUS at initial screening and had no suspicious findings.

The mean and median patient ages were 64.2 and 64 years, respectively, in the Gunma cohort and 61.8 and 61 years, respectively, in the ERSPC Rotterdam cohort. In the former cohort, the mean and median follow-up durations were 2.95 and 3 years, respectively. Of the 2650 participants in the Gunma study, 465 (17.5%), 430 (16.2%), 524 (19.8%), and 1231 (46.5%), respectively, were followed for 1, 2, 3, and 4 years after initial screening. In contrast, all members of the ERSPC Rotterdam cohort were rescreened once, at 4 years after initial screening. At rescreening, DRE and/or TRUS were performed at least once for 2203 patients in the Gunma cohort (83.1%) and for all 747 patients in the Rotterdam cohort who had PSA levels ≥ 3.0 ng/mL (23.6% of the Rotterdam cohort as a whole).

In the Gunma study, biopsy indications changed as follows over the course of the follow-up period (which ran through December 2001): in 1992 and 1993, the cutoff value for PSA level as a biopsy indication was set at 6.0 ng/mL for all age ranges; thereafter, the cutoff value was changed to 3.0 ng/mL for men ages 55–59 years (1994–2001) and men ages 60–64 years (2000–2001), to 3.5 ng/mL for men ages 65–69 years (2000–2001), and to 4.0 ng/mL for men ages 70–74 years (1994–2001). In addition, over the period 1994–1999, the cutoff level was set at 4.0 ng/mL for men ages 60–69 years. In the ERSPC Rotterdam cohort, biopsy was indicated for PSA levels ≥ 4.0 ng/mL and/or abnormal findings on DRE or TRUS through March 1997. Thereafter, the cutoff PSA level was changed to 3.0 ng/mL, regardless of findings on DRE or TRUS. One hundred thirty-five patients with initial PSA levels between 1.0 and 2.9 ng/mL who experienced PSA doubling over the 4-year follow-up period also underwent prostate biopsy (regardless of DRE and TRUS findings) after providing informed consent.

DRE findings were considered abnormal if a nodular lesion, capsular irregularity, or firmness of the prostate was documented. TRUS findings were con-

sidered abnormal if a hypoechoic lesion or capsular irregularity was evident.

In the Gunma study, men with abnormal findings on PSA testing, DRE, and/or TRUS were informed by mail about the necessity of additional urologic examinations. These additional examinations typically included TRUS-guided lateral sextant biopsy and two additional sets of transition zone biopsies (via the transperineal and transrectal routes). Site-directed prostate biopsy also was performed for patients with abnormal findings on DRE and/or TRUS. Alternatively, annual or quarterly PSA measurements were proposed for the follow-up of participants who chose not to undergo additional urologic examination and for whom immediate prostate biopsy was not recommended by a physician at an affiliated hospital. All biopsy specimens in the Gunma study were reviewed by two urologic pathologists from the Department of Pathology, Gunma University School of Medicine (Maebashi, Japan).

In the ERSPC Rotterdam cohort, TRUS-guided systematic sextant biopsy was performed via a transrectal approach. In addition, site-directed prostate biopsy was performed for patients with abnormal findings on DRE or TRUS. Prostate biopsy was recommended for all patients who had abnormal findings on rescreening. All biopsy specimens in the Rotterdam cohort were reviewed by urologic pathologists from the Department of Pathology, Erasmus Medical Center (Rotterdam, The Netherlands).

In the Gunma study, serum PSA levels were measured at the Department of Urology, Gunma University School of Medicine, using the E-Test Tosoh II PA assay in conjunction with an AIA-600 analyzer (Tosoh, Tokyo, Japan). In the Rotterdam Section of the ERSPC, PSA measurements were made at the Department of Clinical Chemistry, Erasmus Medical College, using the Tandem-E PSA assay (Beckman Coulter, Fullerton, CA). The two assays used have been shown to be equimolar in the recognition of free and total PSA in the serum and to yield nearly identical results.[5] The following formula could be used to convert total PSA levels as measured using the Tandem-E assay to total PSA levels as measured using the E-Test Tosoh II assay: $PSA_{Tosoh} = 0.9731 \times PSA_{Tandem} + 0.0361$ ng/mL ($r = 0.9993$ [unpublished data]). Thus, we were able to compare serum PSA values measured by these two assays without making any corrections.

For cases in which follow-up occurred at 2–4 years from baseline, interval PSA levels were estimated using initial and final PSA values and the assumption that PSA levels changed over time in a simple exponential fashion. This procedure was used to estimate interval PSA levels at 1, 2, and 3 years after initial screening for all patients in the Rotterdam cohort. In the Gunma cohort, interval PSA levels were estimated for the 430, 524, and 1231 patients, respectively, who underwent follow-up at 2, 3, and 4 years after initial screening.

TABLE 1
Baseline Data for Men Undergoing Screening for Prostate Carcinoma in the ERSPC Rotterdam and Gunma Studies

Variable	Study: ERSPC Rotterdam	Study: Gunma	Statistical significance
No. of patients	3163	2650	
Age (yrs)			
Mean ± SD	61.8 ± 4.6	64.2 ± 4.4	$P < 0.0001$[a]
Median	61	64	
Range	55–71	55–73	
Age distribution (%)			
55–59 yrs	1308 (41)	347 (13)	$P < 0.0001$[b]
60–64 yrs	970 (31)	1062 (40)	
65–69 yrs	774 (24)	895 (34)	
70–74 yrs	111 (4)	346 (13)	
PSA (ng/mL)			
Mean ± SD	1.5 ± 0.9	1.2 ± 0.8	$P < 0.0001$[a]
Median	1.3	1.0	
PSA distribution (%)			
0.0–0.9 ng/mL	820 (26)	1319 (50)	$P < 0.0001$[b]
1.0–1.9 ng/mL	1542 (49)	907 (34)	
2.0–2.9 ng/mL	522 (17)	294 (11)	
3.0–3.9 ng/mL	279 (9)	130 (5)	

ERSPC Rotterdam: European Randomized Study of Screening for Prostate Cancer, Rotterdam Section; SD: standard deviation; PSA: prostate-specific antigen.
[a]Welch test.
[b]Chi-square test.

Data on patient ages and serum PSA levels at initial screening in both cohorts are presented in Table 1. Differences in these parameters were considered significant when P was less than 0.05 according to the Student t test, the Welch t test, or the χ^2 test. Significant differences in mean patient age and PSA level at initial screening were found. In addition, the proportion of participants in younger age groups and the proportion of participants in higher PSA categories were significantly greater in the Rotterdam cohort than in the Gunma cohort.

In the Rotterdam cohort, probabilities of freedom from prostate carcinoma after a 4-year screening interval were calculated according to age group and PSA range. In contrast, in the Gunma cohort, the cumulative probability of freedom from prostate carcinoma over the course of the 4-year observation period was estimated using the Kaplan–Meier method. Differences between the two cohorts in terms of the likelihood of freedom from prostate carcinoma were as-

TABLE II
Risk of Developing Screen-Detectable Prostate Carcinoma after 4 Years of Follow-Up Observations, Stratified by Age at Initial Screening

Age at initial screening (yrs)	No. of participants at risk: Yrs elapsed after initial screening 1	2	3	4	Risk of prostate carcinoma detection: No. of events observed	Rate of freedom from prostate carcinoma (%)	95% confidence interval	Statistical significance
ERSPC Rotterdam								
55–59	—	—	—	1308	58	95.6	(94.4–96.7)	$P < 0.0001$: ERSPC (all < Gunma (all)
60–64	—	—	—	970	53	94.5	(93.1–96.0)	$P > 0.05$: all comparisons within ERSPC Rotterdam
65–69	—	—	—	774	47	93.9	(92.2–95.7)	$P = 0.0104$: ERSPC (55–59) yrs) < Gunma (55–59 yrs)
70–74	—	—	—	111	6	94.6	(90.3–98.9)	$P = 0.0003$: ERSPC (60–64 yrs) < Gunma (60–64 yrs)
All	—	—	—	3163	164	94.8	(94.0–95.6)	
Gunma study								
55–59	347	295	257	187	1	99.5	(98.4–100)	$P = 0.0047$: ERSPC (65–69 yrs) < Gunma (65—69 yrs)
60–64	1062	897	718	521	9	98.6	(97.7–99.6)	$P > 0.05$: ERSPC (70–74 yrs) = Gunma (70–74 yrs)
65–69	895	767	638	459	13	98.0	(96.8–99.1)	$P = 0.0387$: Gunma (55–59 yrs) > Gunma (70–74 yrs)
70–74	346	226	142	64	5	98.0	(96.1–99.9)	$P > 0.05$: all other comparisons within the Gunma study
All	2650	2185	1755	1231	28	98.4	(97.8–99.0)	

ERSPC Rotterdam: European Randomized Study of Screening for Prostate Cancer, Rotterdam Section.

sessed using the two-sided log-rank test, with the assumption that prostate carcinoma could not be detected during the first 3 years after initial screening in the Rotterdam cohort. Cumulative probabilities of freedom from PSA increases to levels ≥ 4.0 ng/mL during the 4-year observation period also were estimated, with stratification according to age and PSA level, using the Kaplan–Meier method, and cumulative probabilities of freedom from PSA increases to levels ≥ 2.0, 3.0, and 4.0 ng/mL were compared between the Dutch and Japanese cohorts using the two-sided log-rank test.

The prognostic utility of baseline PSA levels, age at initial screening, and geographic location was investigated using Cox proportional hazards modeling. For multivariate analysis, baseline PSA levels were divided into 4 categories (0.0–0.9, 1.0–1.9, 2.0–2.9, and 3.0–3.9 ng/mL), as was patient age at initial screening (55–59, 60–64, 65–69, and 70–74 years).

RESULTS

Of the 3163 men in the ERSPC Rotterdam cohort, 639 (20.2%) had PSA levels ≥ 3.0 ng/mL after 4 years, and 569 of these 639 men underwent prostate biopsy. Another 135 participants (4.3%) who had PSA levels between 1.0 and 2.9 ng/mL had biopsy indicated on the basis of PSA levels alone, in accordance with a side study protocol, and 128 of these participants subsequently underwent prostate biopsy. Thus, a total of 697 patients (22.0%) underwent prostate biopsy at 4 years after initial screening, and prostate carcinoma was detected in 164 (5.2%). Of the 164 patients diagnosed with prostate carcinoma, 79 (48%) and 85 (52%) had PSA levels < 4.0 ng/mL and ≥ 4.0 ng/mL, respectively.

Of the 2650 men in the Gunma cohort, 215 (8.1%) had abnormal findings on DRE and/or TRUS and follow-up PSA levels in the reflex range of 0.0–3.9 ng/mL, and an additional 133 patients (5.0%) had PSA levels ≥ 4.0 ng/mL on follow-up. A total of 133 patients (5.0%) underwent prostate biopsy, and prostate carcinoma was detected in 28 (1.1%; average time from initial screening, 2.6 years). Of the 28 patients diagnosed with prostate carcinoma, 9 (32%) and 19 (68%) had PSA levels < 4.0 ng/mL and ≥ 4.0 ng/mL, respectively.

Table 2 presents cumulative probabilities of freedom from prostate carcinoma according to age at initial screening. The cumulative probability of freedom from prostate carcinoma at 4 years after initial screening was significantly lower in the Rotterdam cohort than in the Gunma cohort for patients ages 55–59, 60–64, and 65–69 years. The overall cumulative probability of freedom from prostate carcinoma at 4 years from baseline also was significantly lower in the Rotterdam cohort (94.8%) than in the Gunma cohort (98.4%).

Cumulative probabilities of freedom from prostate carcinoma according to initial PSA level are presented in Table 3. The likelihood of freedom from prostate carcinoma decreased significantly with increasing initial PSA level in both Dutch and Japanese men. Within each PSA group, the cumulative probability of freedom from prostate carcinoma was lower for Dutch patients compared with Japanese patients, but the difference was not statistically significant.

TABLE III
Risk of Developing Screen-Detectable Prostate Carcinoma after 4 Years of Follow-Up Observations, According to Initial PSA Range

PSA at initial screening (ng/mL)	No. of participants at risk: Yrs elapsed after initial screening 1	2	3	4	Risk of prostate carcinoma detection: No. of events observed	Rate of freedom from prostate carcinoma (%)	95% confidence interval	Statistical significance
ERSPC Rotterdam								
0.0–0.9	—	—	—	820	6	99.3	(98.7–99.9)	$P = 0.0008$: ERSPC (0.0–0.9 ng/mL) > ERSPC (1.0–1.9 ng/mL)
1.0–1.9	—	—	—	1542	43	97.2	(96.4–98.1)	$P < 0.0001$: ERSPC (0.0–0.9 ng/mL) > ERSPC (2.0–2.9 ng/mL), ERSPC (3.0–3.9 ng/mL)
2.0–2.9	—	—	—	522	63	87.9	(85.1–90.8)	$P < 0.0001$: ERSPC (1.0–1.9 ng/mL) > ERSPC (2.0–2.9 ng/mL), ERSPC (3.0–3.9 ng/mL)
3.0–3.9	—	—	—	279	52	81.4	(76.7–86.0)	$P = 0.0116$: ERSPC (2.0–2.9 ng/mL) > ERSPC (3.0–3.9 ng/mL) $P > 0.05$: ERSPC = Gunma (within the same initial PSA ranges)
Gunma study								
0.0–0.9	1319	1095	884	616	1	99.9	(99.8–100)	$P = 0.0036$: Gunma (0.0–0.9 ng/mL) > Gunma (1.0–1.9 ng/mL) > Gunma (2.0–2.9 ng/mL)
1.0–1.9	907	762	615	439	8	98.7	(97.7–99.6)	$P < 0.0001$: Gunma (0.0–0.9 ng/mL) > Gunma (2.0–2.9 ng/mL), Gunma (3.0–3.9 ng/mL)
2.0–2.9	294	235	182	129	9	94.5	(90.8–98.2)	$P < 0.0001$: Gunma (1.0–1.9 ng/mL) > Gunma (3.0–3.9 ng/mL)
3.0–3.9	130	93	74	47	10	88.5	(81.3–95.7)	$P = 0.0193$: Gunma (2.0–2.9 ng/mL) > Gunma (3.0–3.9 ng/mL)

ERSPC Rotterdam: European Randomized Study of Screening for Prostate Cancer, Rotterdam Section; PSA: prostate-specific antigen.

The overall cumulative probability of freedom from PSA increases to levels ≥ 4.0 ng/mL at 4 years from baseline was significantly lower in the Rotterdam cohort than in the Gunma cohort (Table 4). In addition, after stratification according to patient age, the cumulative probability of freedom from such PSA increases was found to be significantly higher for patients ages 55–59 years compared with patients ages 60–64 years and patients ages 65–69 years in the Rotterdam cohort. Likewise, in the Gunma cohort, the cumulative probability of such PSA increases was significantly higher for patients ages 55–59 years compared with patients ages 60–64 years, patients ages 65–69 years, and patients ages 70–74 years. In addition, within each age group, except for patients ages 70–74 years, the cumulative probability of freedom from PSA increases to levels ≥ 4.0 ng/mL was significantly lower in the Rotterdam cohort compared with the Gunma cohort.

PSA-stratified cumulative probabilities of freedom from PSA increases at 4 years after initial screening are presented in Table 5. In both Dutch and Japanese patients, the cumulative probability of freedom from PSA increases to levels ≥ 4.0 ng/mL decreased in the following order with regard to initial PSA range: 3.0–3.9 ng/mL, 2.0–2.9 ng/mL, 1.0–1.9 ng/mL, and 0.0–1.9 ng/mL. The same trend was observed in our analyses of the cumulative probabilities of freedom from PSA increases to levels ≥ 2.0 and 3.0 ng/mL, respectively. Within each PSA group, there was no statistically significant difference between Dutch and Japanese patients in terms of the cumulative probability of freedom from PSA increases.

Table 6 summarizes the results of Cox proportional hazards analysis. Neither age nor geographic location was independently predictive of PSA increases to levels ≥ 4.0 ng/mL. In contrast, initial PSA levels may be significantly predictive of such increases ($P < 0.0001$). Multivariate analysis also revealed that after controlling for age and initial PSA level, Japanese and Dutch patients did not have significantly different risks of experiencing PSA increases to levels ≥ 4.0 ng/mL.

DISCUSSION

To our knowledge, no study to date has investigated the risk of developing prostate carcinoma and having PSA levels ≥ 4.0 ng/mL at 4 years after a negative prostate carcinoma screening examination. Our findings indicate that the risk of developing prostate carcinoma was greater for Dutch men compared with Japanese men within the same age group, and this difference was consistent with the observed differences in age-specific baseline PSA distributions between Dutch and Japanese patients.

The current study compared participants in two different screening trials–one based in Europe and the other based in Japan. Due to underlying differences in screening practices between these two regions, the comparability of cumulative prostate carcinoma incidence data may be limited. Specifically, prostate carcinoma detection rates at 4 years from baseline may

TABLE IV
Cumulative Rates of Freedom from PSA Increases to Levels 4.0 ng/mL or Greater during 4 Years of Observation, Stratified by Age at Initial Screening (exponential model)

	The risk of PSA increase to 4.0 ng/mL or greater										
	No. of participants at risk				No. of events expected						
	Yrs elapsed after initial screening				Yrs elapsed after initial screening						
Age at initial screening (yrs)	1	2	3	4	1	2	3	4	Cumulative rate of freedom from PSA increase (%)	95% Cofidence interval	Statistical significance
ERSPC Rotterdam											
55–59	1308	1294	1273	1240	14	21	33	46	91.3	(89.7–92.8)	$P < 0.0001$: ERSPC (all) < Gunma (all)
60–64	970	947	919	884	23	28	35	24	88.7	(86.6–91.1)	$P = 0.0292$: ERSPC (55–59 yrs) > ERSPC (60–64 yrs)
65–69	774	756	731	698	18	25	33	31	86.2	(83.7–88.7)	$P = 0.0002$: ERSPC (55–59 yrs) > ERSPC (65–69 yrs)
70–74	111	110	106	102	1	4	4	1	91.0	(85.6–96.4)	$P > 0.05$: all other comparisons within ERSPC Rotterdam
All	3163	3107	3029	2924	56	78	105	102	89.2	(88.1–90.3)	
Gunma study											
55–59	347	294	254	183	1	3	2	2	96.9	(94.6–99.1)	$P = 0.0038$: ERSPC (55–59 yrs) < Gunma (55–59 yrs)
60–64	1062	889	702	502	15	18	14	5	93.7	(92.0–95.5)	$P = 0.0004$: ERSPC (60–64 yrs) < Gunma (60–64 yrs)
65–69	895	755	620	441	16	16	16	7	92.2	(90.1–94.2)	$P = 0.0008$: ERSPC (65–69 yrs) < Gunma (65–69 yrs)
70–74	346	222	139	62	11	3	3	1	91.9	(87.5–96.4)	$P > 0.05$: ERSPC (70–74 yrs) = Gunma (70–74 yrs)
All	2650	2160	1715	1188	43	40	35	15	93.4	(92.3–94.5)	$P = 0.0298$: Gunma (55–59 yrs) > Gunma (60–64 yrs) $P = 0.0051$: Gunma (55–59 yrs) > Gunma (65–69 yrs) $P = 0.0052$: Gunma (55—59 yrs) > Gunma (70–74 yrs) $P > 0.05$: all other comparisons within the Gunma study

ERSPC Rotterdam: European Randomized Study of Screening for Prostate Cancer, Rotterdam Section; PSA: prostate-specific antigen.

have been biased by the following factors: 1) differences in screening modalities used; 2) differences in the PSA cutoff levels selected as indications for biopsy; 3) differences in biopsy methods used; 4) differences in compliance with biopsy recommendations among patients with abnormal findings; and 5) differences in histologic criteria between the ERSPC and Gunma studies.

With regard to initial screening methods, all participants in the Rotterdam cohort underwent screening via PSA testing, DRE, and TRUS; in contrast, 37.2% of all participants in the Gunma cohort (986 of 2650) did not undergo TRUS at study entry. Thus, patients who would have had abnormal findings on TRUS may have been enrolled in the current study. In the Rotterdam Section of the ERSPC, 8.6% of all men who had PSA levels < 4.0 ng/mL and normal findings on DRE (447 of 4727) had abnormal findings on TRUS. Among these 447 patients, prostate carcinoma was detected in 38 (data not shown), corresponding to a 0.8% prevalence of prostate carcinoma among patients with normal DRE findings and PSA levels < 4.0 ng/mL. This rate should not be used for the statistical adjustment of findings made in the Gunma cohort, however, because of the observed differences between Japanese and Dutch men in terms of baseline PSA distribution. Three additional participants in the Gunma study who had PSA levels in the reflex range of 3.1–4.0 ng/mL and no suspicious findings on DRE and/or TRUS and who were subsequently diagnosed with prostate carcinoma were excluded from the current study because of recent age-specific changes in PSA-related biopsy indications. Nonetheless, overall, it appears that the recruitment bias encountered in the current study was not substantial.

TABLE V
Cumulative Rates of Freedom from Prostate Carcinoma and PSA Increases During 4 Years of Observation, According to Initial PSA Range (exponential model)

	PSA levels on consecutive screens (ng/mL)								
	≥2.0			≥3.0			≥4.0		
PSA at initial screening (ng/mL)	No. of events expected	Cumulative rate of freedom from PSA increase (%)	95% confidence interval	No. of events expected	Cumulative rate of freedom from PSA increase (%)	95% confidence interval	No. of events expected	Cumulative rate of freedom from PSA increase (%)	95% confidence interval
ERSPC Rotterdam									
0.0–0.9	20	97.6	(96.5–98.6)	5	99.4	(98.9–99.9)	5	99.4	(98.9–99.9)
1.0–1.9	506	67.2	(64.8–69.6)	146	90.5	(89.0–92.0)	53	96.6	(95.6–97.5)
2.0–2.9	—	—		271	48.1	(43.7–52.5)	124	76.2	(72.5–80.0)
3.0–3.9	—	—		—	—		159	43.0	(37.1–48.9)
Gunma study									
0.0–0.9	22	97.3	(96.2–98.5)	7	99.3	(98.7–99.9)	5	99.6	(99.2–99.95)
1.0–1.9	204	72.4	(69.0–75.9)	49	91.6	(89.2–94.0)	20	96.6	(95.1–98.2)
2.0–2.9	—	—		105	54.3	(47.1–61.5)	50	74.6	(68.1–81.1)
3.0–3.9	—	—		—	—		58	46.8	(36.6–57.1)
Statistical significance	$P < 0.0001$: ERSPC (0.0–0.9 ng/mL) > ERSPC (1.0–1.9 ng/mL) $P < 0.0001$: Gunma (0.0–0.9 ng/mL) > Gunma (1.0–1.9 ng/mL) $P > 0.05$: ERSPC = Gunma (within the same initial PSA ranges)			$P < 0.0001$: ERSPC (0.0–0.9 ng/mL) > ERSPC (1.0–1.9 ng/mL) > ERSPC (2.0–2.9 ng/mL) $P < 0.0001$: Gunma (0.0–0.9 ng/mL) > Gunma (1.0–1.9 ng/mL) > Gunma (2.0–2.9 ng/mL) $P > 0.05$: ERSPC = Gunma (within the same initial PSA ranges)			$P < 0.0001$: ERSPC (0.0–0.9 ng/mL) > ERSPC (1.0–1.9 ng/mL) > ERSPC (2.0–2.9 ng/mL) > ERSPC (3.0–3.9 ng/mL) $P = 0.0001$: Gunma (0.0–0.9 ng/mL) > Gunma (1.0–1.9 ng/mL) $P < 0.0001$: Gunma (0.0–0.9 ng/mL) > Gunma (2.0–2.9 ng/mL) > Gunma (3.0–3.9 ng/mL) $P < 0.0001$: Gunma (1.0–1.9 ng/mL) > Gunma (2.0–2.9 ng/mL) > Gunma (3.0–3.9 ng/mL) $P > 0.05$: ERSPC = Gunma (within the same initial PSA ranges)		

ERSPC Rotterdam: European Randomized Study of Screening for Prostate Cancer Rotterdam Section; PSA: prostate-specific antigen.

TABLE VI
Significance of Parameters for Predicting PSA Progression Using the Cox Proportional Hazards Model

Factor	Subdivided groups being compared	Regression coefficient	*P* value
Age (yrs)	55–59 vs. 60–64 vs. 65–69 vs. 70–74	−0.001	0.986
Baseline PSA level (ng/mL)	0.0–0.9 vs. 1.0–1.9 vs. 2.0–2.9 vs. 3.0–3.9	1.595	< 0.0001
Region	Gunma vs. Rotterdam	−0.08	0.451

PSA: prostate-specific antigen.

PSA cutoff levels did not differ dramatically between the Dutch and Japanese cohorts. Furthermore, although the biopsy procedures used in these two studies differed with regard to the route taken, the effects of this difference may have been minimized by the introduction of TRUS-guided sextant biopsy in both cohorts, provided that similar numbers of biopsy cores were obtained from Dutch and Japanese patients; consistent with this provision, the number of biopsy cores to be obtained from the peripheral zone was set at 6 in both the Rotterdam cohort and the Gunma cohort.

Although it appears that differences in screening modalities, PSA cutoff levels, and biopsy methods can be disregarded, variations in terms of compliance with biopsy recommendations may represent the most serious barrier to the accurate estimation of cumulative probabilities of freedom from prostate carcinoma. Among patients in the Rotterdam cohort who had PSA levels ≥ 3.0 ng/mL, the proportion who underwent

prostate biopsy was relatively high (89% [569 of 639]). In contrast, of the men in the Gunma cohort who had PSA levels ≥ 4.0 ng/mL or abnormal findings on DRE and/or TRUS, only a relatively small proportion (38% [133 of 348]) underwent biopsy. This discrepancy in terms of compliance rates may stem from differences in follow-up strategies and study policies between Europe and Japan. Due to the low rate of compliance with biopsy recommendations, the rate of prostate carcinoma detection may have been underestimated in the Gunma study. In the Rotterdam cohort, prostate biopsy was recommended for all patients with abnormal findings on PSA testing, DRE, and/or TRUS, and biopsy was performed for all such patients except for those who had severe complications or were receiving anticoagulant therapy. Thus, using data from the Rotterdam cohort, it would be possible to estimate the number of prostate carcinoma cases that went undetected in men who did not undergo prostate biopsy despite having abnormal findings on PSA testing, DRE, and/or TRUS. In the Gunma study, for men who had abnormal findings on DRE or TRUS, prostate biopsy tended to be performed immediately after it was recommended, especially for those whose PSA levels fell between the age-specific reference cutoff level and 10 ng/mL; therefore, it would be difficult, using PSA distributions alone, to estimate the number of prostate carcinoma cases that went undetected among men with abnormal findings on PSA testing who did not undergo biopsy.

We were able to calculate the cumulative likelihood of freedom from PSA increases in both the Dutch and Japanese cohorts, with interval PSA levels being estimated using an exponential model. The probability of a PSA increase to levels ≥ 4.0 ng/mL may be indicative of a patient's risk of developing prostate carcinoma, although the percentage of patients who experience such PSA increases exceeds the actual prevalence of prostate carcinoma, because of the possibility of non-malignancy-related increases in PSA levels.[6] Nonetheless, comparison of the Dutch and Japanese cohorts with regard to the percentages of patients experiencing PSA increases to levels ≥ 4.0 ng/mL (rather than with regard to the cumulative probability of prostate carcinoma detection) is likely to yield a more accurate estimate of the true relative cumulative likelihood of developing prostate carcinoma in each of these two cohorts. Comparisons of this type are objective and allow us to ignore differences in screening modalities, PSA testing cutoff levels, differences in prostate biopsy procedures, and, most importantly, significant differences in patient compliance with biopsy recommendations.

With regard to the concern that there may have been differences in histologic criteria between the Gunma study and the Rotterdam Section of the ERSPC, all histologic review of biopsy specimens in both cohorts was performed by urologic pathologists. Although interobserver variability in terms of Gleason grading may have been present, bias with regard to the diagnosis of cases as malignant or nonmalignant by urologic pathologists in Japan or the Netherlands would have been unlikely.

Only 28 cases of prostate carcinoma were found in the Gunma cohort, and when stratification according to baseline PSA or 5-year age range was performed, no stratum contained more than 13 cases. Thus, there may not have been adequate power to compare Dutch and Japanese patients within each stratum, although significant differences were found between the two cohorts in terms of the cumulative likelihood of freedom from prostate carcinoma at 4 years after initial screening for patients ages 55–59 years, patients ages 60–64 years, and patients ages 65–69 years. In contrast, comparisons of cumulative rates of freedom from PSA increases to levels ≥ 4.0 ng/mL within each age group may have had adequate statistical power. Rates of freedom from such increases were significantly lower in the Rotterdam cohort than in the Gunma cohort for patients ages 55–59 years, patients ages 60–64 years, and patients ages 65–69 years. Among patients ages 70–74 years, however, there was no significant difference between the two cohorts in terms of the cumulative rate of freedom from such increases, just as there was no significant difference in the cumulative probability of freedom from prostate carcinoma within this age group. Taken together, these results confirm that the risk of developing prostate carcinoma is significantly higher for 55–69-year-old Dutch men with no suspicious findings on PSA testing or DRE than for their Japanese counterparts. Epidemiologic surveys have revealed similar trends with regard to prostate carcinoma incidence in Japan and the Netherlands; the age-adjusted incidence of prostate carcinoma among Japanese males is 11.1 per 100,000, compared with 55.9 per 100,000 among Dutch males.[7] Based on rates of freedom from PSA increases, the cumulative probabilities of developing prostate carcinoma within a given 4-year period were 2.8 and 1.8 times greater for Dutch men compared with Japanese men within the 55–59-year-old and 60–69-year-old age groups, respectively. In contrast, PSA increases were equally likely for Dutch males and Japanese males ages 70–74 years. Thus, differences in prostate carcinoma incidence between the Netherlands and Japan may be growing smaller with increasing age.

Cumulative rates of freedom from both prostate

carcinoma detection and PSA increases did not differ significantly within initial PSA range groups between the Rotterdam and Gunma cohorts. These results confirm that the risk of developing screen-detectable prostate carcinoma may be the same for European and Japanese men with the same baseline PSA levels. Multivariate analysis also revealed that the cumulative probability of PSA increases to ≥ 4.0 ng/ml was not significantly different between the Dutch and Japanese cohorts after controlling for age and PSA levels at initial screening. Therefore, differences in the cumulative probability of developing prostate carcinoma within the 55–69-year-old age group may originate from higher baseline PSA levels in Dutch men compared with Japanese men.

The exponential phase of PSA elevation was shown to begin 7–9 years before clinical tumor detection.[8] Therefore, patients in the current study who were found to have prostate carcinoma may have already harbored minute, but potentially active, prostate carcinomas at initial screening. Yatani et al.[9] demonstrated that the prevalence of latent prostate carcinoma was 1.5 times higher in white U.S. men (34.6%) compared with Japanese men (20.5%). When those investigators subdivided latent prostate carcinoma cases into two groups according to pathologic features (latent infiltrative or latent noninfiltrative), the prevalence of the former type reflected the overall prevalence of clinical malignancy. The findings made in the current study demonstrate that the risk of developing screen-detectable prostate carcinoma is expected to be 1.8 times higher for Dutch men compared with Japanese men within the 60–69-year-old age range. Therefore, the difference in cumulative rates of PSA increases to levels ≥ 4.0 ng/ml may have originated from the difference in the prevalence of latent infiltrative prostate carcinoma. Although the probability of having potentially active prostate carcinoma may increase with increasing baseline PSA levels, this probability does not appear to differ between Dutch and Japanese men within the same baseline PSA category. Once an active tumor, even if minute, has developed, the risk of developing screen-detectable disease may be the same for Dutch and Japanese men. It is hypothesized that the difference in prostate carcinoma incidence between men in European countries and those in Asian countries may result from the difference in the promotion process up until the development of these minute tumors. Furthermore, it may be possible to predict relative differences in prostate carcinoma development between any pair of nations, provided that large screening databases of baseline PSA levels are available.

In conclusion, within the 55–69-year-old age range, the cumulative probability of developing prostate carcinoma over a 4-year observation period was 1.8–2.8 times higher in Dutch males without any suspicious findings compared with their Japanese counterparts. The cumulative probability of developing prostate carcinoma significantly increased with increasing baseline PSA in both nations, and prostate carcinoma risk appeared to be equivalent for Dutch and Japanese males within each baseline PSA group.

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CUMULATIVE PROBABILITY OF PSA INCREASE ABOVE 4.0 NG/ML IN POPULATION-BASED SCREENING FOR PROSTATE CANCER

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Routine screening for prostate cancer remains controversial. However, it is very important to show how the optimal rescreening interval should be set for men who want to be screened after informed consent. To solve this issue, the risk of prostate-specific antigen (PSA) increase above 4.0 ng/ml relative to baseline PSA levels and age was investigated. Between 1988 and 2000, 7,757 subjects screened twice or more and also with baseline PSA levels of 4.0 ng/ml or lower were enrolled in our study. All serum PSA levels were measured by E-test Tosoh II PA assay at one center. Interval PSA levels for men undergoing screening with a greater than 1 year interval were calculated on the assumption that PSA levels changed over time in a simple exponential fashion. Then, the cumulative rate of freedom from PSA increase above 4.0 ng/ml was estimated using the Kaplan-Meier technique stratified by baseline PSA ranges of 0.0 to 1.0, 1.1 to 2.0, 2.1 to 3.0 and 3.1 to 4.0 ng/ml and every 10 years of age ranges. Of the 7,757 subjects, 559 (7.2%) were expected to have had PSA levels increase above 4.0 ng/ml within 5 years after the baseline PSA measurements. The cumulative rate of freedom from the PSA increase above 4.0 ng/ml at 5 years was 98.7%, 92.9%, 70.3% and 38.5% in cases of baseline PSA levels of 1.0 ng/ml or lower, 1.1 to 2.0 ng/ml, 2.1 to 3.0 ng/ml and 3.1 to 4.0 ng/ml, respectively. The cumulative rates of freedom from the PSA increase were significantly decreased with the baseline PSA ranges being higher regardless of age range. Re-screening interval should be set stratified by baseline PSA levels, regardless of age and race. Rescreening interval should be set at 1, 1 to 2 and 3 to 5 years for men with baseline PSA ranges of 2.1 to 4.0 ng/ml, 1.1 to 2.0 ng/ml and 0.0 to 1.0 ng/ml, respectively, in individual-based screening. In mass screening system using PSA alone, rescreening interval should be set in the same manner as in individual-based screening, except for men with baseline PSA levels of 1.1 to 2.0 ng/ml, which should be set at 1 year to avoid developing incurable prostate cancer.
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Key words: *PSA; screening interval; prostate cancer*

As the most frequently diagnosed cancer and the second leading cause of cancer death in most Western countries, prostate cancer represents a significant healthcare problem. One of the best hopes to decrease mortality for prostate cancer has resulted in the wide use of screening regimens based on prostate-specific antigen (PSA) for asymptomatic men. However, screening and management of subsequently diagnosed prostate cancer can be harmful to individuals. In this situation, there is obvious need to provide conclusive information prior to the application of screening tests to men who hope to have information on screening.[1] At the same time, it is very important to propose an optimal screening program for well-informed participants on screening.

It is widely known that the probability of prostate cancer is strongly related to the serum PSA levels.[2,3] Therefore, it would be very important to investigate the risk of PSA increase in men with baseline PSA levels of 4.0 ng/ml or lower. In the present study, we investigated the cumulative risk of PSA increase not only relative to baseline PSA levels but also relative to age ranges in order to propose how and when the optimal rescreening interval should be set.

MATERIAL AND METHODS

A population-based study of screening for prostate cancer in Gunma Prefecture has been performed since 1981. Between 1981 and 1991, digital rectal examination (DRE) and prostatic acid phosphatase (PAP) were used as screening modalities. After 1992, PSA-based screening has been carried out for all participants. DRE and transrectal ultrasonography (TRUS) were also performed as ancillary tests in most municipalities until 1994. Then, the number of municipalities that conducted DRE and TRUS has decreased each year in the past 5 years because a PSA test had usually been conducted in conjunction with a basic health check-up system using a blood test only, which is conducted by local government and is also spread throughout Japan.

Between 1992 and 2000, 13,021 men, 50 to 79 years old, had PSA levels measured in population-based screening for prostate cancer in Gunma prefecture, Japan. Of these, 12,058 (92.6%) had initial PSA levels of 4.0 ng/ml or less. In addition, 2,447 men in the same age range underwent initial screening using digital rectal examination (DRE) and prostatic acid phosphatase between 1988 and 1991, and had PSA levels of 4.0 ng/ml or less by retrospective PSA measurements using frozen serum (−70°C). Of these 14,505 men with initial PSA levels of 4.0 ng/ml or less, 8,012 (55.2%) had not been rescreened until December 2000 and could not been followed in our population-based screening system. The remaining 6,493 (44.8%), who underwent screening twice or more, were enrolled in our study. The age range at initial screening was from 50 to 78 years old (63.5±6.4; mean±S.D.), and the number of screenings ranged from 2 to 13 (mean; 3.6) during 1 to 14 (mean; 4.1) years of observations.

All serum PSA levels were measured using E-test Tosoh II assay with the AIA-600 machine (Tosoh, Tokyo, Japan) at one center (the Department of Urology, Gunma University School of Medicine). The screening for prostate cancer has been performed by local governments, and subjects were invited by letter or by announcement, which included the fact sheet on screening for prostate cancer from the public health care center, and participated in the screening study based on this advertisement.

Figure 1 shows the number of participants enrolled at initial screening and the number of cases with PSA changes from the lower to higher range during observations. Baseline PSA levels were subdivided into 4 groups: 0.0–1.0 ng/ml, 1.1–2.0 ng/ml, 2.1–3.0 ng/ml and 3.1–4.0 ng/ml. Then, baseline PSA was defined as initial PSA levels or PSA levels increased to higher PSA ranges for the first time. For example, when PSA levels have changed in the order of 0.2, 1.2 and 0.5 ng/ml, the first and second PSAs of 0.2 and 1.2 ng/ml are eligible for baseline PSAs, but the third PSA of

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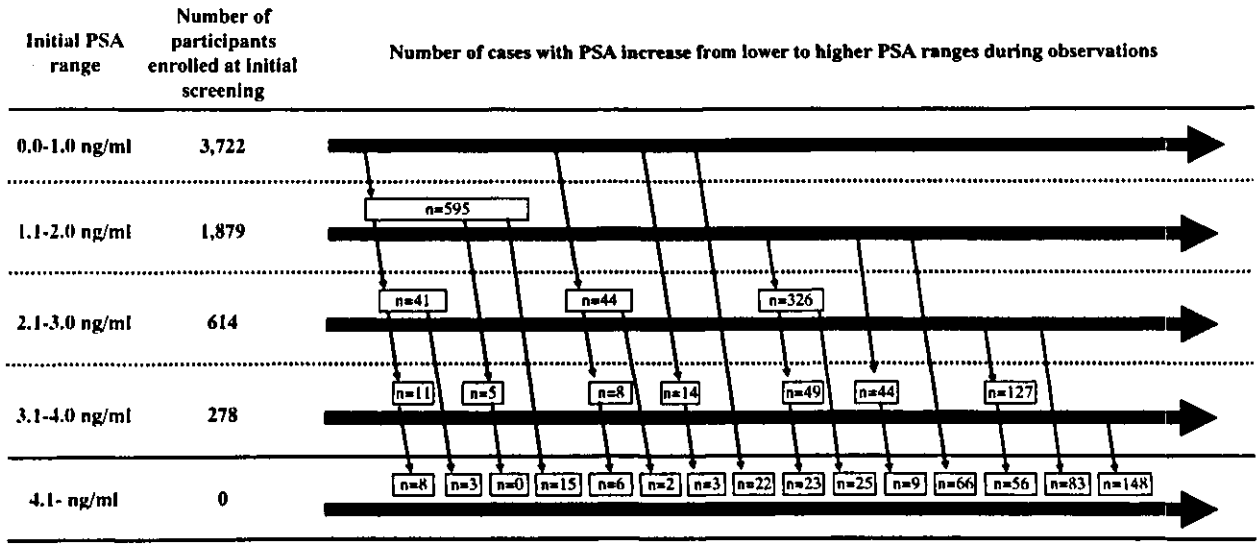

FIGURE 1 – The number of cases at initial screening in each PSA category, changes in the PSA levels during observation periods and the number of men with PSA levels of 4.1 ng/ml or greater at actual screening.

0.5 ng/ml is not. Individuals whose PSA levels had changed gradually from lower to higher PSA ranges below 4.0 ng/ml were considered as a different risk set. Therefore, 7,757 cases were enrolled for estimating cumulative risk of PSA increase above 4.0 ng/ml stratified by baseline PSA and age ranges (Fig. 1).

For cases screened with a rescreening interval of greater than 1 year, interval PSA levels were estimated by yearly units on the assumption that PSA levels had changed over time in a simple exponential fashion. When a case had the most recent PSA level ($PSA_{most\ rec.}$) measured at x years after the baseline PSA (PSA_{base}) measurement, the interval PSA level ($PSA_{int.}$) at y year(s) after the PSA_{base} measurement could be calculated using the following formula:

$$\log_{10} PSA_{int.} = (\log_{10} PSA_{most\ rec} - \log_{10} PSA_{base})/x \times y + \log_{10} PSA_{base}.$$

For estimating cumulative rate of freedom from PSA increase, a time to PSA increase above 4.0 ng/ml was defined as the time between baseline PSA measurement and actual PSA or $PSA_{int.}$ level increased to 4.1 ng/ml or greater for the first time.

PSA data of men 80 years or older in consecutive screening were excluded from our study. The end point of our study was set at the time of PSA increase above 4.0 ng/ml for the first time. PSA distributions were compared by chi-square test. Cumulative rates of freedom from PSA increase were estimated by Kaplan-Meier techniques and were compared using 2-sided log-rank tests. Differences were considered significant when p was <0.05.

RESULTS

The detailed number of cases with PSA levels of 4.1 or greater is shown in Figure 1. Of the 6,493 subjects who participated in our study, 469 (7.2%) had PSA levels increased to 4.1 ng/ml or greater. Among the 7,757 in the risk group divided by baseline PSA levels, 667 (8.6%) showed PSA levels had increased above 4.0 ng/ml at the actual screening. Of these 667 cases with the PSA increase, 133, 109, 113, 85, 70 and 157 showed PSA level increases above 4.0 ng/ml at 1, 2, 3, 4, 5 and 6 or more years after the baseline PSA measurements, respectively.

The change in the median and maximum PSA levels during 5 years, stratified by age range and baseline PSA levels, are shown in Table I. The median PSA levels were similar in the same baseline PSA range throughout the observation periods for 5 years. Table I also shows the percentage of cases with PSA levels greater than 4.0 ng/ml during 5 years of observations. In men with baseline PSA levels of 0.0 to 1.0 ng/ml, the percentage of cases with PSA levels greater than 4.0 ng/ml in all age ranges were between 0.0% and 0.7%. The percentage of cases with PSA levels greater than 4.0 ng/ml did not increase with time ($p>0.05$, $\chi 2$ test). In men with baseline PSA levels of 1.1 to 2.0 ng/ml, the percentage of cases with PSA levels greater than 4.0 ng/ml in all age ranges were between 0.6% and 3.9%. There was a significant relation between the percentage of cases with PSA levels greater than 4.0 ng/ml and the elapsed years in the same age range ($p<0.05$, $\chi 2$ test). In men with baseline PSA levels of 2.1 to 3.0 ng/ml, the percentage of cases with PSA levels greater than 4.0 ng/ml in all age ranges was relatively high between 4.0% and 12.8% and increased with time. There was a significant relation between the percentage of cases with PSA levels greater than 4.0 ng/ml and the elapsed time in the same age range ($p<0.05$, $\chi 2$ test). In men with baseline PSA levels of 3.1 to 4.0 ng/ml, the percentage of cases with PSA levels greater than 4.0 ng/ml in all age ranges were high between 20.5% and 32.2%. There was no significant relation between the elapsed time and the percentage of cases with PSA levels greater than 4.0 ng/ml during 5 years of observation ($p>0.05$, $\chi 2$ test).

After calculating interval PSA levels using the exponential model, 559 (7.2 %) were expected to have had PSA levels increased above 4.0 ng/ml within 5 years after the baseline PSA measurements. Of these 559 cases, 206, 147, 107, 54 and 45 cases were expected to have a PSA increase at 1, 2, 3, 4 and 5 years after the baseline PSA measurements, respectively.

The cumulative rates of freedom from PSA increase relative to age and baseline PSA ranges during 5 years of observations are shown in Table II. The overall cumulative rate of freedom from the PSA increase was 89.5% at 5 years after the baseline PSA measurements. The cumulative rates of freedom from the PSA increase in all baseline PSA range of 0.0 to 4.0 ng/ml were significantly different among the age ranges of 50 to 59, 60 to 69 and 70 to 79 years. The cumulative rates of freedom from the PSA increase in all age ranges were significantly decreased with baseline PSA

TABLE I - THE MEDIAN, MAXIMUM PSA LEVELS AND THE PERCENTAGE OF CASES WITH PSA LEVELS GREATER THAN 4.0 NG/ML AT ACTUAL SCREENING STRATIFIED BY AGE, BASELINE PSA LEVELS AND YEARS ELAPSED AFTER THE BASELINE PSA MEASUREMENTS

Years elapsed	Age range (years old)	Baseline PSA range (ng/ml) 0.0–1.0 PSA levels (ng/ml) Median	Maximum	Percent cases with PSA >4 ng/ml	1.1–2.0 PSA levels (ng/ml) Median	Maximum	Percent cases with PSA >4 ng/ml	2.1–3.0 PSA levels (ng/ml) Median	Maximum	Percent cases with PSA >4 ng/ml	3.1–4.0 PSA levels (ng/ml) Median	Maximum	Percent % cases with PSA >4 ng/ml
1	50–59	0.7	10.0	0.2%	1.3	6.1	0.4%	2.2	7.5	2.6%	3.3	5.4	15.4%
	60–69	0.7	7.4	0.3%	1.4	9.5	1.7%	2.3	12.7	4.8%	3.2	14.8	20.1%
	70–79	0.7	7.3	0.2%	1.4	6.9	0.3%	2.3	5.6	3.0%	3.1	6.2	22.2%
	All	0.7	10.0	0.3%	1.3	9.5	1.1%	2.3	12.7	4.0%	3.2	14.8	20.5%
2	50–59	0.7	13.8	0.9%	1.4	5.2	0.5%	2.3	3.7	0.0%	2.9	5.4	28.6%
	60–69	0.7	12.4	0.6%	1.4	11.7	0.5%	2.5	7.0	7.0%	3.3	15.5	25.4%
	70–79	0.7	3.9	0.0%	1.4	4.7	1.1%	2.3	5.2	4.7%	3.4	39.1	27.5%
	All	0.7	13.8	0.6%	1.4	11.7	0.6%	2.4	7.0	5.6%	3.3	39.1	26.4%
3	50–59	0.7	2.9	0.0%	1.4	3.7	0.0%	2.5	5.2	12.2%	2.7	7.5	25.0%
	60–69	0.8	14.8	0.5%	1.5	15.3	2.1%	2.5	39.1	12.8%	3.5	12.1	32.2%
	70–79	0.7	3.9	0.0%	1.4	6.4	1.7%	2.6	6.6	10.7%	3.5	7.7	34.1%
	All	0.7	14.8	0.3%	1.4	15.3	1.7%	2.5	39.1	12.3%	3.5	12.1	32.2%
4	50–59	0.7	3.2	0.0%	1.4	5.8	1.6%	2.5	6.4	14.8%	2.4	5.7	12.5%
	60–69	0.7	3.9	0.0%	1.5	39.1	3.6%	2.6	14.4	12.9%	3.5	6.4	26.7%
	70–79	0.7	2.8	0.0%	1.6	1,928	1.6%	2.7	8.5	11.1%	3.2	9.6	32.1%
	All	0.7	3.9	0.0%	1.5	1,928	3.0%	2.6	14.4	12.7%	3.3	9.6	27.1%
5	50–59	0.7	4.8	0.4%	1.4	6.7	3.8%	2.3	5.7	8.3%	2.3	3.5	0.0%
	60–69	0.8	10.4	0.7%	1.6	13.3	3.1%	2.7	1,289	10.4%	2.8	150.3	31.1%
	70–79	0.7	22.7	0.8%	1.5	6.7	8.6%	2.7	8.1	23.7%	3.3	8.1	23.1%
	All	0.7	22.7	0.7%	1.5	13.3	3.9%	2.7	1,289	12.8%	2.8	150.3	28.3%

ranges being higher, which were 98.7%, 92.9%, 70.3% and 38.5% in men with baseline PSA levels of 0.0 to 1.0 ng/ml, 1.1 to 2.0 ng/ml, 2.1 to 3.0 ng/ml and 3.1 to 4.0 ng/ml, respectively. The cumulative rates of freedom from PSA increase within the same baseline PSA range were not significantly different among the age ranges of 50 to 59, 60 to 69 and 70 to 79 years, except one subgroup with the baseline PSA range of 1.1 to 2.0 ng/ml and age range of 50 to 59 years. On the other hand, the cumulative rates of freedom from PSA increase within the same age range were significantly different among the baseline PSA ranges of 0.0 to 1.0 ng/ml, 1.1 to 2.0 ng/ml, 2.1 to 3.0 ng/ml and 3.1 to 4.0 ng/ml.

DISCUSSION

The age-adjusted incidence of prostate cancer in Japanese males is very low, approximately 10 in 100,000 compared to 147.3 in Caucasian Americans and 222.9 in African-Americans[4] by epidemiological studies. Furthermore, during the period of 1988–1992, the average age-adjusted incidence rates of prostate cancer in native Japanese and Japanese-Americans in Los Angeles were 9.0 and 47.2 per 100,000, respectively.[5] The difference in the age-adjusted incidence rate between the 2 groups has been considered to be related to the different lifestyle characteristics in USA and Japan. However, there may be differences in the cancer registry systems and screening systems among different countries. The increasing incidence in Americans may reflect the more intensive screening for prostate cancer in the USA than that in Japan.

Alternatively, serum PSA measurement has been widely accepted to detect early stage of prostate cancer, and levels in the serum are strongly related to the possibility of prostate cancer. There was only one comparative study on serum PSA levels among Japanese-American and native Japanese males.[6] They compared the age-specific PSA levels and estimated the prevalence of undetected prostate cancer in the 2 populations. They suggested that estimated cancer prevalence in males who were 75 years old was 10.0% and 5.4% in American-Japanese and native Japanese, respectively. They asserted that Japanese-American males showed increased risk to have prostate cancer in comparison with native Japanese in Japan but less than the findings reported by some epidemiological studies.[4,5]

It is of interest to compare the cumulative rate of PSA increase above 4 ng/ml in men with baseline PSA levels of 4.0 ng/ml or lower. The 5 years cumulative risks of PSA increase above 4 ng/ml in Americans were 1.6%, 7.6%, 34.6% and 83.0% in men with baseline PSA levels of 0.0 to 1.0 ng/ml, 1.1 to 2.0 ng/ml, 2.1 to 3.0 ng/ml and 3.1 to 4.0 ng/ml, respectively.[7] In the present study, the cumulative rates of PSA increase above 4.0 ng/ml at 5 years also increased when baseline PSA ranges were higher, which were 1.3%, 7.1%, 29.7% and 71.5% in men with baseline PSA levels of 0.0 to 1.0 ng/ml, 1.1 to 2.0 ng/ml, 2.1 to 3.0 ng/ml and 3.1 to 4.0 ng/ml, respectively. The future risk of PSA increase in the same baseline PSA range may be similar to that between Americans and Japanese men.

However, there were some limitations and flaws in the present study. First, almost half of the first screened men did not undergo consecutive screening. This low percentage of men undergoing screening twice or more may lead to self-selection bias. The mean age of men screened only once were significantly older and the baseline PSA levels of those men were significantly lower than those of 6,493 men screened twice or more (data not shown). However, we analyzed the cumulative rate of freedom from PSA increase stratified by baseline PSA and age ranges, so the flaw from self-selection bias in our study may be ignored.

Second, the lack of uniformity in screening interval may lead to a serious flaw about changes in PSA. Therefore, we estimated interval PSA levels for all men who underwent screening with greater than a 1 year interval on the assumption that PSA levels changed over time in a simple exponential fashion. Therefore, the percentage of cases with PSA levels that were greater than 4.0 ng/ml in each year may be corrected more precisely.

Third, the lack of information on screening outcomes was also a limitation in our study. The cumulative rates of PSA increase may overestimate the true risk of developing prostate cancer in the future because an unknown part of the PSA increase may have originated from benign prostatic disease. On the other hand, the cumulative rate of screen detectable prostate cancer may underestimate the true risk of developing prostate cancer because of the likelihood of missing cancer. Recently, Ito *et al.*[8] demonstrated the natural history of PSA increase in men with and without prostate cancer. The probability of noncancer-related PSA increase was high at about 90% if cases had baseline PSA levels of 2.0 ng/ml or less and also had PSA increase within 2 years. On the other hand, the probability of noncancer-related PSA increase was relatively

TABLE II - THE CUMULATIVE RATES OF FREEDOM FROM PSA INCREASE STRATIFIED BY AGE RANGE AND BASELINE PSA LEVELS

Age range (years old)	Baseline PSA range (ng/ml)	Number of cases at risk	Number of event observed	Cumulative rate of freedom from PSA increase above 4.0 ng/ml (standard error)					Statistical significance
				1	2	3	4	5	
50–59	0.0–1.0	979	8	99.9% (0.1%)	99.4% (0.3%)	99.4% (0.3%)	99.4% (0.3%)	98.5% (0.6%)	Age (50–59) $p = 0.03$: PSA (0.0–1.0) > PSA (1.1–2.0) $p < 0.0001$: PSA (0.0–1.0). PSA (1.1–2.0) > PSA (2.1–3.0) > PSA (3.1–4.0) Age (60–69) $p < 0.0001$: PSA (0.0–1.0) > PSA (1.1–2.0) > PSA (2.1–3.0) > PSA (3.1–4.0) Age (70–79) $p < 0.0001$: PSA (0.0–1.0) > PSA (1.1–2.0) > PSA (2.1–3.0) > PSA (3.1–4.0) All Age ranges $p < 0.0001$: PSA (0.0–1.0) > PSA (1.1–2.0) > PSA (2.1–3.0) > PSA (3.1–4.0) PSA (0.0–1.0) $p = 0.91$: Age (50–59) = Age (60–69) $p = 0.32$: Age (50–59) = Age (70–79) $p = 0.23$: Age (60–69) = Age (70–79) PSA (1.1–2.0) $p = 0.04$: Age (50–59) > Age (60–69) $p = 0.04$: Age (50–59) > Age (70–79) $p = 0.98$: Age (60–69) = Age (70–79) PSA (2.1–3.0) $p = 0.14$: Age (50–59) = Age (60–69) $p = 0.21$: Age (50–59) = Age (70–79) $p = 0.72$: Age (60–69) = Age (70–79) PSA (3.1–4.0) $p = 0.89$: Age (50–59) = Age (60–69) $p = 0.82$: Age (50–59) = Age (70–79) $p = 0.85$: Age (60–69) = Age (70–79) All PSA ranges $p < 0.0001$: Age (50–59) > Age (60–69), Age (70–79) $p = 0.0081$: Age (60–69) > Age (70–79)
	1.1–2.0	423	9	99.8% (0.2%)	99.4% (0.4%)	99.1% (0.6%)	97.0% (1.2%)	95.6% (1.5%)	
	2.1–3.0	116	15	98.3% (1.2%)	96.0% (2.0%)	85.3% (4.2%)	77.2% (5.4%)	77.2% (5.4%)	
	3.1–4.0	38	16	68.4% (7.5%)	58.2% (8.4%)	53.3% (9.0%)	53.3% (9.0%)	53.3% (9.0%)	
	All	1,556	48	99.0% (0.3%)	98.1% (0.4%)	96.9% (0.5%)	96.2% (0.6%)	95.1% (0.7%)	
60–69	0.0–1.0	2,124	20	99.8% (0.1%)	99.4% (0.2%)	99.1% (0.2%)	99.1% (0.2%)	98.6% (0.3%)	
	1.1–2.0	1,520	71	99.0% (0.3%)	98.1% (0.4%)	96.0% (0.6%)	94.4% (0.7%)	92.6% (0.9%)	
	2.1–3.0	636	128	95.9% (0.8%)	88.0% (1.4%)	80.1% (1.8%)	74.1% (2.1%)	70.1% (2.4%)	
	3.1–4.0	328	154	75.0% (2.4%)	54.5% (3.0%)	47.2% (3.3%)	41.9% (3.5%)	37.7% (3.7%)	
	All	4,608	373	97.2% (0.2%)	94.4% (0.4%)	91.9% (0.5%)	90.4% (0.5%)	88.9% (0.6%)	
70–79	0.0–1.0	619	2	99.8% (0.2%)	99.8% (0.2%)	99.8% (0.2%)	99.4% (0.5%)	99.4% (0.5%)	
	1.1–2.0	531	18	99.6% (0.3%)	98.3% (0.7%)	97.4% (0.9%)	93.7% (1.7%)	90.7% (2.4%)	
	2.1–3.0	273	40	97.8% (0.9%)	91.4% (2.0%)	82.3% (3.1%)	76.2% (3.9%)	65.0% (5.4%)	
	3.1–4.0	170	78	69.4% (3.5%)	56.7% (4.1%)	45.9% (4.8%)	43.8% (5.0%)	35.9% (6.5%)	
	All	1,593	138	96.2% (0.5%)	93.3% (0.7%)	90.5% (0.9%)	88.0% (1.1%)	84.7% (1.4%)	
All	0.0–1.0	3,722	30	99.8% (0.1%)	99.5% (0.1%)	99.2% (0.2%)	99.2% (0.2%)	98.7% (0.3%)	
	1.1–2.0	2,474	98	99.2% (0.2%)	98.3% (0.3%)	96.8% (0.4%)	94.8% (0.6%)	92.9% (0.7%)	
	2.1–3.0	1,025	183	96.7% (0.6%)	89.8% (1.1%)	81.0% (1.5%)	75.4% (1.8%)	70.3% (2.0%)	
	3.1–4.0	536	248	72.8% (1.9%)	55.9% (2.4%)	47.5% (2.6%)	42.4% (2.8%)	38.5% (3.0%)	
	All	7,757	559	97.3% (0.2%)	94.9% (0.3%)	92.6% (0.3%)	91.1% (0.4%)	89.5% (0.5%)	

PSA: prostate specific antigen, Age (50–59): age range of 50–59 years, Age (60–69); age range of 60–69 years. Age (70–79): age range of 70–79 years, PSA (0.0–1.0): baseline PSA range of 0.0–1.0 ng/ml, PSA (1.1–2.0); baseline PSA range of 1.1–2.0 ng/ml, PSA (2.1– 3.0); baseline PSA range of 2.1–3.0 ng/ml, PSA (3.1–4.0); baseline PSA range of 3.1–4.0 ng/ml

low at about 50% for cases who had baseline PSA levels of 2.1 to 4.0 ng/ml or had PSA increase after 3 years of baseline PSA measurements.

Finally, men with a gradual PSA increase from lower to upper baseline PSA category were counted multiple times in the present study. Of those men, some patients with PSA increase above 4.0 ng/ml may have been counted multiple times; then, this methodology might inflate the risk of PSA increase in the PSA range of 1.1 to 4.0 ng/ml. Therefore, we compared the risk of PSA increase above 4.0 ng/ml between cases classified into each baseline PSA range at initial screening and those done in consecutive screening. However, the cumulative rate of freedom from PSA increase in men with baseline a PSA range of 1.1 to 2.0 ng/ml or with 2.1 to 3.0 ng/ml at initial screening was not significantly different from that in those with the same baseline PSA category in consecutive screening (data not shown). The 5-year cumulative rate of freedom from PSA increase was significantly lower at 35.1% in men with baseline PSA levels of 3.1 to 4.0 ng/ml at initial screening than those with in consecutive screening, which was 44.0% ($p=0.02$) (data not shown). Therefore, persons who got counted multiple times according to the inclusion criteria may not inflate the estimates in the risk of PSA increase above 4.0 ng/ml in the baseline PSA reflex range of 1.1 to 4.0 ng/ml.

The risk of PSA increase at 1 year after the baseline PSA measurement was relatively high at 3.3% and high at 27.2% in men with baseline PSA levels of 2.1 to 3.0 ng/ml and 3.1 to 4.0 ng/ml, respectively. Furthermore, the probability of cancer related PSA increase in men with baseline PSA levels of 2.1 to 4.0 ng/ml was high at 1 year after baseline PSA measurements.[8] Therefore, we recommend annual screening using PSA measurements and DRE to minimize the delay in prostate cancer detection for individual-based screening. On the other hand, several studies demonstrated the validity of lower PSA cut-offs. Catalona *et al.*[9] demonstrated that the rates of organ-confined cancer were 81%, 70%, 71% and 53% for PSA reflex ranges of 2.6 to 4.0 ng/ml, 4.1 to 5.0 ng/ml, 5.1 to10 ng/ml and greater than 10 ng/ml, respectively, in 676 patients treated with radical prostatectomy. Furthermore, regardless of the DRE findings, the positive predictive value of PSA levels of 2.5 to 4.0 ng/ml[10] was unexpectedly high at 25%. Catalona *et al.*[11] also demonstrated that the positive predictive value of prostate cancer in subjects with PSA levels of 2.5 to 4.0 ng/ml and without abnormal findings on DRE was relatively high at 15%. They also demonstrated the possibility of using cut-off points for the free/total PSA ratio to identify men at relatively high risk of prostate cancer in this reflex range of PSA. Therefore, when a mass screening for prostate cancer is conducted using PSA measurement alone, lowered cut-offs of PSA can detect more organ-confined cancers compared to a cut-off of 4.0 ng/ml. However, lowered cut-offs for all participants require more biopsies, and they may detect more insignificant cancers.[12,13] Then, we should use lower cut-offs for PSA in combination with other serum markers like free/total PSA ratio[11] or should set cut-offs for PSA in an age-specific manner.[14]

In men with baseline PSA levels of 1.1 to 2.0 ng/ml, the cumulative risk of PSA increase above 4.0 ng/ml was relatively low at 0.8% and 1.7% at 1 and 2 years after the baseline PSA measurement. In this baseline PSA range, the probability of noncancer-related PSA increase was high at 86% within 2 years after baseline PSA measurements.[8] On the other hand, the 3 years cumulative risk of rising PSA increased to 3.2%, and the probability of noncancer-related PSA increase lowered to 55% between 3 and 4 years after the baseline PSA measurement.[8] Furthermore, a previous study also suggested that the proportion of clinical T3N0M0 disease in prostate cancer cases detected after a rescreening interval of 3 years was high in the baseline PSA range of 1.1 to 2.0 ng/ml.[15] Therefore, the rescreening interval using the PSA measurement should be set within 2 years.

In our study, 1 case who did not undergo DRE at the baseline PSA measurement had a huge PSA increase from 1.6 ng/ml to 1,927 ng/ml after a rescreening interval of 4 years. The interval PSA levels were expected to be 6.6 ng/ml and 43.9 ng/ml at 1 and 2 years after the baseline PSA measurement, respectively. Therefore, setting of a 2-year rescreening interval for men with baseline PSA range of 1.1 to 2.0 ng/ml may result in increasing the risk of incurable prostate cancer in mass screening system using PSA alone. On the other hand, there was no case with a huge PSA increase within 5 years in men with the same baseline PSA range and also with normal baseline DRE findings (data not shown). Therefore, rescreening interval can be set at 1 or 2 years in individual-based screening using both PSA and DRE. Alternatively, rescreening interval in mass screening using PSA alone should be set at 1 year to avoid developing incurable prostate cancer.

In men with baseline PSA levels of 1.0 ng/ml or lower, the cumulative rate of PSA increase above 4.0 ng/ml was low during 5 years of observations. The probability of cancer-related PSA increase may be extremely low within 2 years after the baseline PSA measurement.[8] However, the 3-year cumulative risk of PSA increase was 0.8% in the present study, and the probability of cancer related PSA increase among men with increasing PSA above 4.0 ng/ml at 3 years after the baseline PSA measurement increased to 20%.[8] Furthermore, the cumulative risk of PSA increase was 1.3% during 5 years of observation, and the probability of cancer related PSA increase at 5 years after the baseline PSA measurement was relatively high at about 40%.[8] Therefore PSA test should be conducted every 3 years or more but no more than 5 years. In this low baseline PSA range, DRE may still have an important role for detecting prostate cancer because only 14% of prostate cancer cases detected within 5 years after the baseline PSA measurement had PSA abnormality.[15] Therefore, both PSA and DRE should be conducted in individual-based screening.

At present, screening and management of subsequently diagnosed prostate cancer can be harmful to individuals. To solve controversies regarding the screening for prostate cancer, prospective randomized controlled trials are currently on going in the USA[16] and Europe.[17,18] In this situation, there is obvious need to provide informed consent prior to the application of screening tests to men who hope to undergo screening.[1] At the same time, we should construct an optimal screening system for well-informed participants on screening. Furthermore, when we evaluate the usefulness of screening for prostate cancer with regard to mortality rate, quality of life and cost effectiveness, the establishment of an optimal screening system must also be important. The setting of an optimal rescreening interval is considered one of the most important issues not only to influence the efficacy of screening for prostate cancer but also to be informative for participants in the present screening system. Rescreening intervals have been proposed between 1 and 4 years by several organizations and clinical trials.[16-20] More studies are necessary to confirm the optimal screening intervals. However, the present findings could demonstrate some important suggestions that the future risk of prostate cancer may be similar in men with the same baseline PSA levels between Americans and Japanese.

CONCLUSIONS

The probability of PSA increase was not significantly related to age range and may be similar between Americans and Japanese in the same baseline PSA ranges. Therefore, the rescreening interval should be set based on baseline PSA levels. In individual-based screening using both PSA and DRE, the rescreening interval should be set at 1 year and 1 to 2 years in men with baseline PSA ranges of 2.1 to 4.0 ng/ml and 1.1 to 2.0 ng/ml, respectively. The rescreening interval in mass screening system using PSA alone should be set at 1 year for men with baseline PSA ranges of 1.1 to 4.0 ng/ml. The risk of rapid PSA increase may be low in men with baseline PSA levels of 0.0 to 1.0 ng/ml, so the rescreening interval should be set between 3 and 5 years.

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Characteristics of Patients with Prostate Cancer Who Have Initially been Treated by Hormone Therapy in Japan: J-CaP Surveillance

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Objective: Hormone therapy for prostate cancer has empirically prevailed in Japan. We planned to evaluate the trends and outcome of hormone therapy for establishing an adequate guideline.

Methods: Patients with prostate cancer who were initially treated by hormone therapy were registered through the J-CaP registration system. This report summarizes the background factors.

Results: From January 2001 to October 2003, 17 872 patients were registered from 395 institutes throughout Japan. The background factors of 17 312 patients were analyzed. The 17 872 patients were estimated as composing more than half of newly diagnosed prostate cancer patients in Japan. Of these, 22.9, 35.1, 32.9 and 8.6% belonged to T1, T2, T3 and T4, respectively. For the purposes of hormone therapy, 77.5% was primary hormone therapy. Neoadjuvant setting and adjuvant setting were 18.1 and 4.3%, respectively. About 60% of the hormone therapy was combined hormone therapy with LH-RHa plus anti-androgens.

Conclusion: Irrespective of patients' age, TNM, stage of illness, or histological background, the majority of prostate cancer patients in Japan are receiving hormone therapy. It is necessary to evaluate whether this trend is merely a continuation of past experience of Japanese urologists or if there is a difference in the profile of effect and side-effect in the case of Japanese patients compared to therapy given in Westerners.

Key words: prostate cancer – hormone therapy – endocrine therapy

INTRODUCTION

In prostate cancer treatment, hormone therapy has been used in Europe and North America mainly to provide temporary relief for advanced cancers. However, the CaPSURE report (1), released in 2003, indicates that there is a rapid increase in the use of hormone therapy on localized cancer in the United States, which suggests a drastic change in the role of hormone therapy. Meanwhile, in Japan, hormone therapy has been used over many years in a considerable number of patients with localized or locally advanced prostate cancer. In recent years, while clinical trial data (2,3) indicating its usefulness have been accumulating, the outcomes have yet to be accurately analyzed. As typically seen in the early prostate cancer (EPC) studies of recent years in Europe and North America (4), clinical trials are being reported that point to the effectiveness of hormone therapy in localized cancer (5,6). Against this backdrop, in 2001 the Japan Study Group of Prostate Cancer (J-CaP Study Group) was inaugurated with financial support from the Japan Kidney Foundation. This project has been authorized by the Japan Urological Association. The purposes of this study group were to gather information about the hormone therapy administered to Japanese prostate cancer patients living in Japan and to analyze the outcomes of treatment in order to create a guideline for optimal hormone therapy. This report summarizes the background factors of patients receiving hormone therapy across most of Japan.

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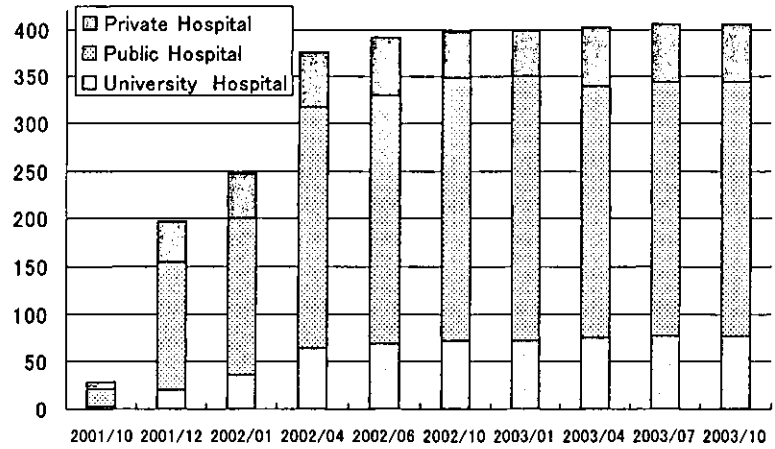

Figure 1. Overview of the year of registration and type of institution.

PATIENTS AND METHODS

The rules for the J-CaP study group are summarized in the Appendix.

Eligible Institutions

Eligible institutions are Japanese urological institutions endorsing the purpose of this study that are able to obtain the approval of their own ethics committees (or IRB). Institutions that have not yet established their own ethics committee (or IRB) but can be vetted instead by an affiliated institution or can obtain approval from the person responsible for the institution are also included. As a rule, in each eligible institution, all cases of patients newly starting hormone therapy for prostate cancer in and after January 2001 will be regarded as subjects of the study.

Period of Research

Registration will commence when approval is obtained from the J-CaP Study Group. The term of case registration is for 3 years and the follow-up period is for 2 years.

Method

Data under the following headings for each registered case will be relayed to the secretariat server over the Internet: date of birth, family history, date of PSA reading, PSA value, PSA kit name, testosterone value, biopsy date, Gleason score, histological grade, clinical stage, case history, details of hormone therapy, whether or not there has been progress observation, whether or not surgery was carried out, date of surgery, operative procedure, whether or not radiotherapy is being conducted, irradiation method, irradiation date, progress. TNM classification used was the 5th edition (7). Histological grade and other criteria were adopted in accordance with the Japanese Urological Association/Japan Society of Pathology 3rd Edition of General Rules for Clinical and Pathological Studies on Prostate Cancer (8).

Follow-up Method

The registered cases, as a rule, are to be updated once every 3 months with regard to test data, change in treatment and progress data. The secretariat immediately contacts institutions not updating information, requesting data input. The secretariat forwards input forms for data addition, and confirms registered cases as of that date as necessary. Additionally, assistance can be given on adding test data and entering changes in treatment and progress data.

This report concerns patient background factors, tumor factors and treatment details of registered cases between 2001 and October 2003.

RESULTS

Participating Institutions

By October 2003, 395 institutions throughout Japan had registered, acquiring IDs and passwords. Eleven institutions of the 395 later withdrew registration. Fig. 1 gives an overview of the year of registration and type of institution. The number of university hospitals registering was 76 (60.2% of university hospitals in Japan); in detail, 35 national university hospitals (83.3%) have been included.

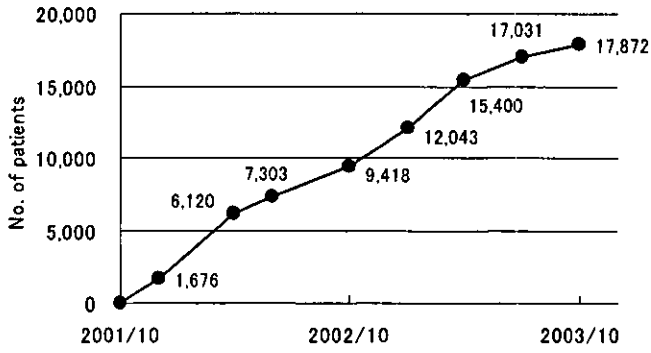

Figure 2. Cumulative number of patients registered.