Tokai J Exp Clin Med., Vol. 30, No. 2, pp. 103-110, 2005

Screening program of prostate cancer at Tokai University Hospital: Characterization of prostate-specific antigen measurement

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(Received February 28, 2005; Accepted March 28, 2005)

A total of 67,214 men participated in screening for prostate cancer (PC) using serum prostate-specific antigen (PSA) from April 1996 to March 2003 at Tokai University Hospital. In 3.5% (2,330/67,214) of the men, an elevated PSA level (>4.0 ng/ml) was found and 68.1% (1,586/2,330) of these subjects were examined at our Urological Outpatient Clinic. Re-testing of PSA showed that 8.4% (133/1,586) had a normal level. Needle biopsy of the prostate was performed in 45.2% (633/1,453) of the remaining men. As a result, 142 PCs were found and the detection rate was 0.2% (142/67,214). The age of the patients with PC was over 50 years. During this period, 135 individuals with voiding dysfunction were also diagnosed as having PC. Comparison of the patients detected by screening with those found at the outpatient clinic revealed significant differences of the age (64.8 vs. 71.9 years, $p<0.0001$), serum PSA level (14.6 vs. 154.9 ng/ml, $p<0.0001$), and clinical stage ($p<0.0001$). In conclusion, a health screening program that includes serum PSA testing is useful for detection of PC at an earlier stage and in younger individuals. We recommend that all men aged 50 years or older undergo testing for PSA to detect PC at an early stage.

Key words: health screening, prostate cancer, PSA

INTRODUCTION

Prostate cancer (PC) is the second leading cause of male death due to malignancy in most industrialized countries [1]. Although the incidence of PC is still not as high in Japan as in the USA or European countries, it has been increasing steadily [2-4]. In Japan, there were 12,969 PC patients in 1996 and PC accounted for 4.7% (12,969/274,171) of all cancers. Accordingly, PC was the 6th most common malignancy in Japanese men, following cancers of the stomach, lung, colon, liver, and rectum [5]. The number of PC deaths has increased fourfold over the past 30 years, and a further threefold increase in both the incidence and death from this cancer is anticipated by 2015 [6, 7]. In comparison with other cancers, PC has shown a greater increase in its incidence and death rate. Therefore, early detection is required to improve the chance of cure.

The increased diagnosis of PC has been largely attributed to the widespread introduction of testing for prostate-specific antigen (PSA). In 1986, PSA was first approved for the detection of recurrence in patients with an established diagnosis of PC. Soon after, the potential of this test for early detection was recognized. It is now widely accepted that the risk of PC is closely related to the serum PSA level and that testing for

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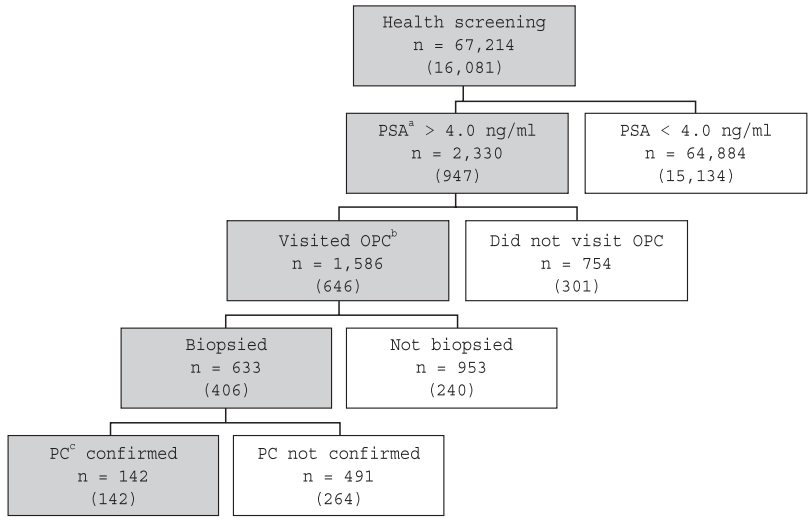

Fig. 1 Flow chart of screening using serum PSA[a] at Tokai University Hospital from April 1996 to March 2003. For 8 years, among 16,081 male participants based on abnormal PSA levels, 142 were histologically diagnosed as having prostatic adenocarcinoma.

PSA is the basis for diagnosis of this cancer [8]. Mass screening for PC based on serum PSA levels was initiated in Japan at the Kyoto Prefectural University of Medicine in 1975, followed by the Gunma Oncology Screening Group in Gunnma University in 1981. Over 50 institutions were participating in PC mass screening by 1999 [9, 10].

Our hospital established an institution for thorough medical screening in 1975 [11], and since February 1977 digital rectal examination (DRE) by urologists was used in a multiphase health screening program for detection of possible PC. Then serum PSA testing was introduced into the screening program from April 1996 for all male examinees aged 45 years and over. Between April 1996 and March 2003, 67,214 men participated in the health screening program, resulting in the detection of abnormal PSA levels in 3.5% and diagnosis of PC in 0.2% (Fig. 1). In this study, the profile of the men with PC and the significance of screening for this cancer were investigated. The age, PSA level at diagnosis, and clinical tumor stage were compared between men with PC detected by screening and those diagnosed as having PC at the outpatient clinic after presenting with urinary symptoms.

SUBJECTS AND METHODS

Subjects

Between April 1996 and May 2003, 67,214 individuals (the number of subjects 16,081) with a mean age of 55.1 years (range: 45 to 93 years) participated in multiphase health screening at Tokai University Hospital. Serum PSA levels were measured to detect PC. The age distribution of the men was shown in Fig. 2.

A total of 2,330 (3.5%) examinees had an abnormal serum PSA level (>4.0 ng/ml). The abnormal PSA rates in each age group were shown in Fig. 3. Of the 2,330 participants with elevated PSA levels, 1,586 (68.1%) were examined at our Urological Outpatient Clinic. Re-testing of PSA showed normal readings in 8.4% (133/1,586) of them. The rates for each age group of examinees with normal level on re-testing of PSA were showed in Fig. 4. One thousand four hundred fifty-three examinees showed abnormal PSA levels on re-testing, and needle biopsy of the prostate was performed in 633 of them (43.6%).

Among the 633 examinees underwent biopsy, 142 (22.4%) were histologically diagnosed as having prostatic adenocarcinoma. Thus, the detection rate was

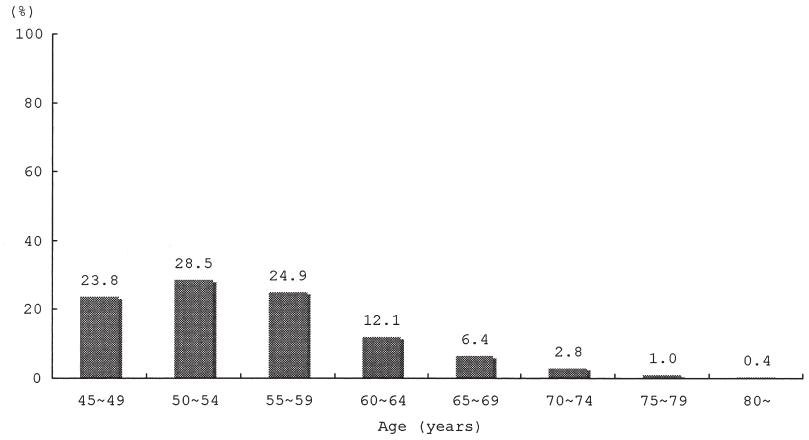

Fig. 2 Age distribusion. The participation rate was highest for examinees in 50s, and second highest was for those aged from 45 to 49 years.

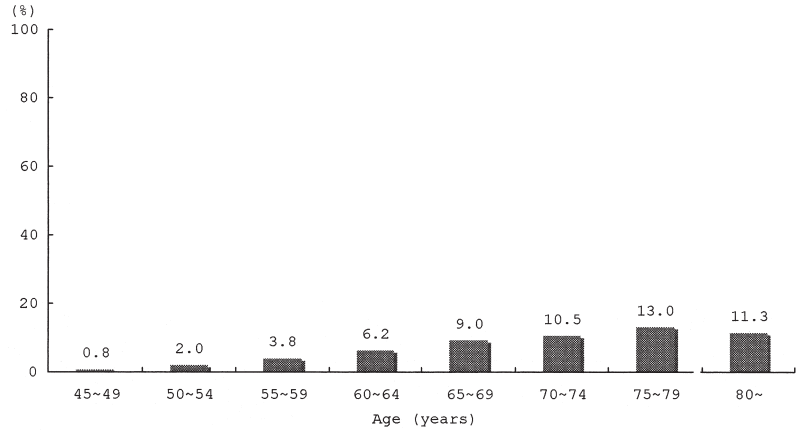

Fig. 3 Detection rate of abnormal PSA level versus age. Abnormal PSA levels by screening tended increase steadily with age.

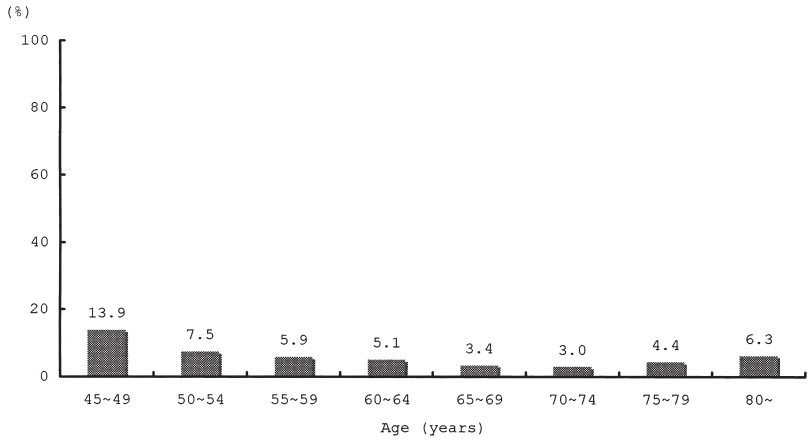

Fig. 4 Detection rate of a normal PSA level on re-testing versus age. The rate of examinees with a normal PSA level on re-testing was relatively high among men aged 45 to 49 years, and decreased steadily with age until 74 years. But from 75 years, it steadily increased again.

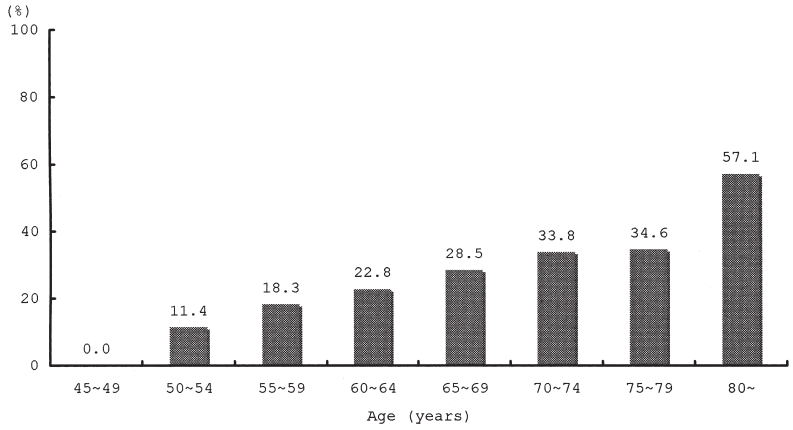

Fig. 5 Positive biopsy rate versus age. Positive biopsy rate steadily increased from 50 years with age. The rate of the examinees aged 80 years or older was strikingly high.

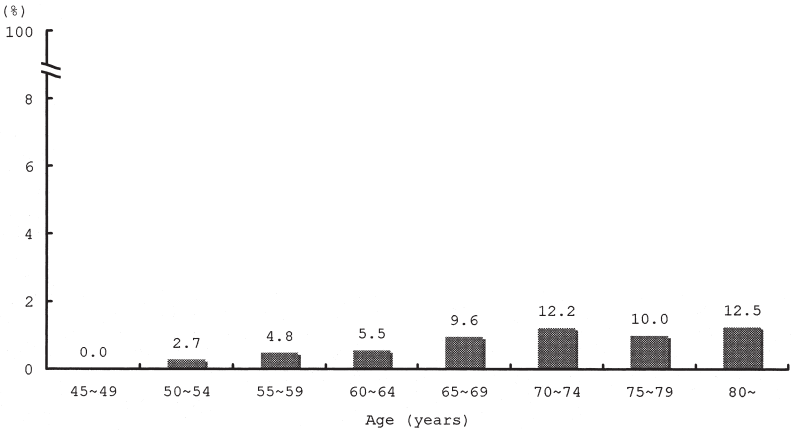

Fig. 6 PC detection rate in examinees with obnormal PSA levels versus age. The detection rate of PC based on abnormal PSA levels also gradually increased from 50 years according to age, and then the rate became plateau in examinees aged 70 years or older.

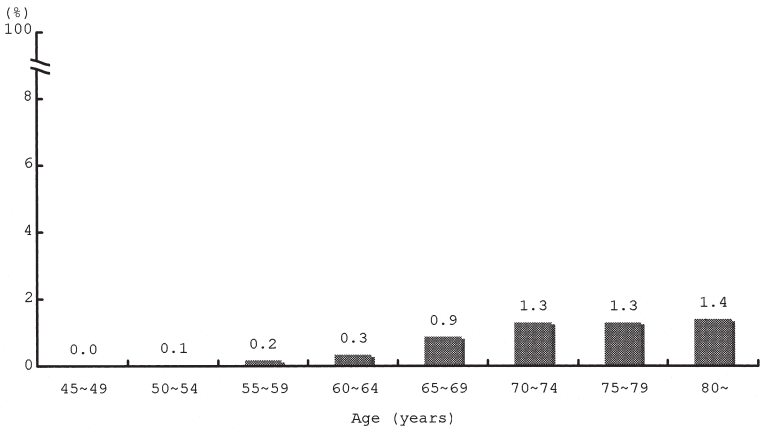

Fig. 7 Overall PC detection rate versus age. The overall PC detection rate gradually increased from 50 years according to age until 64 years. From 65 years the rate significantly increased and became plateau in those aged 70 years or older.

0.2% (142/67,214) among all of the screening tests, or 0.88% (142/16,081) of the subjects. Two cases were evaluated as highly suspicious of adenocarcinoma and there were 4 cases of atypical hyperplasia. The positive biopsy rates in each age group were shown in Fig. 5. The detection rates of PC in each age group based on abnormal PSA levels at screening were shown in Fig. 6. The overall detection rates of PC in each age group were shown in Fig. 7.

Outpatients

During this period, 155 individuals with voiding dysfunction were diagnosed as having PC at the outpatient clinic because the prostate was abnormal on DRE and/or the serum PSA level was elevated (>4.0 ng/ml). Among them, 20 were excluded because the PSA level at diagnosis and/or clinical stage was unavailable, so a total of 135 men were compared with those detected by the screening program.

PSA measurement and diagnosis

The serum PSA level was measured at an outside laboratory (SRL inc., Tokyo, Japan) using a MARKIT-M PA kit (Dainihon-Pharmaceutial, Osaka, Japan) until December 1998, while a Tosoh Ⅱ assay (Eiken, Tokyo, Japan) has been used since January 1999. The PSA measurement was carried out at the Department of Laboratory Medicine of Tokai University Hospital. MARKIT-M PSA data were not interconverted because they are considered to be virtually the same as those of the Tosoh Ⅱ PSA [12]. The serum PSA level was used for screening and all of the examinees with abnormal PSA level (>4.0 ng/ml) were referred for further urological evaluation. Digitally guided, systemic random core or directed needle biopsy of the prostate was performed until March 2002. Up to six specimens were obtained in a biopsy. Transrectal ultrasound (TRUS)-guided systemic biopsy has been performed since April 2002. Eight specimens were obtained in a biopsy. When PC was confirmed histologically, the clinical stage was determined in accordance with the unified TNM system using the results of DRE, TRUS and/or magnetic resonance imaging, computed tomography, and bone scintigraphy [13]. The subjects who had a negative biopsy were followed with repeated PSA measurement every 3 to 6 months at our Urological Outpatient Clinic and re-biopsy was performed when their PSA level increased more or when PC was highly suspected by DRE and/or TRUS findings.

Statistical analysis

Patient characteristics and clinical findings were compared between the positive biopsy group with confirmation of PC and the negative biopsy with no confirmation of PC from the health screening population, and were also compared between PCs detected by screening and PCs detected at the outpatient clinic.

Statistical analysis was performed with JMP In 5.1.1 software (SAS Institute Inc., USA). Continuous variables were tested by Wilcoxon's t-test and nominal variables were analyzed using the χ^2 test. Differences with a probability of less than 0.05 were considered significant.

RESULTS

1. Comparison between the positive and negative biopsy groups

Among 633 examinees who underwent biopsy, 142 (22.4%) were positive with confirmation of PC. Their ages ranged from 50 to 88 years (mean: 64.8), and their serum PSA levels ranged from 4.0 to 377.8 ng/ml (mean: 14.6) (Table). The other 491 examinees (77.6%) had negative biopsy results with no confirmation of PC. Their ages ranged from 45 to 87 years (mean: 60.8), and their serum PSA levels ranged from 4.0 to 44.8 ng/ml (mean: 7.4). Comparison between the positive biopsy and the negative biopsy groups revealed significant differences of the age and PSA levels (both $p<0.0001$). The patients were older and PSA levels were higher in the former group.

2. PC detected by health screening

Among 142 PCs detected by health screening, the clinical stage was $T_{1c}N_xM_x$ in 68 (47.9%), $T_2N_xM_x$ in 67 (47.3%), and $T_{3\text{-}4}N_xM_x/T_{1\text{-}4}N_xM_1$ in 7 (4.9%) (Table). Among these patients, 128 (90.1%) were treated and followed at our hospital. Prostatectomy was performed in 76 patients, endocrine therapy was given to 43 patients, external radiotherapy was given to 4 patients, and 5 patients were simply monitored. One patient died from recurrence of PC after prostatectomy, and one patient who

Table Comparison between PC[a] detected by health screening vs. in the outpatient clinic.

	Screening	Outpatient clinic	*P value*
No. of PC	142	135	
Age in years (range)	64.9 ±7.6 (50~88)	71.9 ±7.5 (55~89)	<0.0001[c]
PSA[b] ng/ml (range)	14.6 ± 33.0 (4.0~377.8)	154.9 ± 477.8 (3.3~4818.0)	<0.0001[c]
Tumor stage (%)			
$T_{1c}N_xM_0$	68 (47.9)	25 (18.5)	<0.0001[d]
$T_2N_xM_0$	* 67 (47.2)	# 41 (30.4)	
$T_{3-4}N_xM_x$ / $T_{1-4}N_xM_1$	7 (4.9)	69 (51.1)	

[a]; prostate cancer
[b]; prostate-specific antigen
[c]; Wilcoxon's t-test
[d]; between * and # by the χ^2 test

received endocrine therapy died of gastric cancer. Fourteen patients were followed by other hospitals 5; 5 of them underwent prostatectomy, 4 received radiation therapy (brachytherapy), and 3 received high-intensity focused ultrasound. No information was obtained for the remaining 2 patients.

3. Comparison between PC detected by screening or at the outpatient clinic

Among 135 PC patients with voiding dysfunction detected at the outpatient clinic, the age ranged from 55 to 89 years (mean: 71.9), and the serum PSA level ranged from 3.3 to 4818.0 ng/ml (mean: 154.9). The clinical stage was $T_{1c}N_xM_x$ in 25 patients (18.5%), $T_2N_xM_x$ in 41 patients (30.4%), and $T_{3-4}N_xM_x/T_{1-4}N_xM_1$ in 69 patients (51.1%). Comparing clinical findings between patients detected by screening and those identified at the outpatient clinic, there were significant differences of the age, serum PSA level, and the clinical stage ($p<0.0001$, Table).

DISCUSSION

In recent years, concern about the public health consequences of PC has been increasing and PSA-based screening for PC at health screening facilities has been performed regularly in Japan. According to the annual report of the Japanese Foundation for Prostate Cancer, the PC detection rate of PSA testing was 0.17% during screening from 1989 to 1999 [10]. The age distribution of the examinees was as follows: 19.3% were aged 45 to 49 years, 22.7% were 50 to 54, 20.8% were 55 to 59; 11.7% were 60 to 64, 5.8% were 65 to 69, 2.2% were 70 to 74, 0.8% were 75 to 79, and 0.2% were 80 or older. PC was detected in 0.006% of those aged 45 to 49 years, while the rates were 0.05% for 50 to 54 years, 0.14% for 55 to 59 years, 0.35% for 60 to 64 years, 0.76% for 65 to 69 years, 0.97% for 70 to 74 years, 1.17% for 75 to 79 years, and 2.27% for 80 years or older [10]. The age distribution of the examinees and the detection rates for each age group in the present study were similar to those previously reported. The participation rate was highest for examinees in their 50s', and the second highest rate was for those in the 40s'. The detection rate of PC in examinees aged 40 to 49 years was extremely low, but the rate became significantly higher in the 50s and then steadily increased with age. In this study, although an abnormal PSA level (>4.0 ng/ml) was found in 0.7% of the examinees aged 45 to 49 years, no PC was detected among them. The rate of examinees with normal PSA level after re-testing was relatively high in this population, showing a gradual decrease with aging and a gradual increase again from 75 years onwards. Ito *et al.* reported that a non-cancer-related increase of PSA was most often caused by prostatic inflammation [14]. Thus PSA normalization at the time of re-testing is speculated to be associated with inflammatory disorders of the prostate because younger individuals (especially men aged 45 to 49 years) are still sexually active

and because the risk of urinary tract infection is higher in elderly individuals due to urinary dysfunction.

The National Research Project on the Efficacy of Mass Screening for Prostate Cancer published official recommendations for a mass screening system in Japan [15]. According to these recommendations, the subjects were to be men over the age of 55 years, because this age group covers almost 99% of patients with clinically significant PC in Japan [15]. The American Cancer Society and the American Urological Association have recommended annual screening for PC in men over 50 years old [16, 17]. For men at high risk of developing PC, such as black men and those with a family history of the cancer, the recommended age to commence screening should be 40 years. An optimal mass screening system has not been established yet with regard to the screening interval impact on quality of life, and cost effectiveness [18]. We consider that it is unnecessary for all men aged 45 to 49 years to participate in PSA testing as screening for PC. It is important that informed consent is obtained prior to performing a screening test in the case of all men who participate in health screening programs irrespective of their age [19].

The serum PSA level is strongly correlated with the presence of PC [20, 21]. In this study, there was a significant difference of PSA levels between the positive biopsy with confirmation of PC and negative biopsy with no confirmation of PC groups. Mäkinen *et al*. compared tumor characteristics between the screening and control arms of a Finnish population-based screening trial performed in the period between 1996 and 1998 [22]. He reported that 82% of cancers in the screening arm were clinically organ-confined versus 65% in the control arm. The median PSA level was substantially lower among cases detected by screening (7.1 μg/L) than among controls (13.2 μg/L). Kato *et al*. [23] also reported that earlier cancer was found by screening in Mitaka City than by diagnosis at the outpatient clinic of Kyorin University Hospital. Furthermore, we demonstrated that the age, PSA level, and clinical stage of patients detected by screening was better compared with those of patients diagnosed at the outpatient clinic. At present, the usefulness of mass screening for PC using PSA is not clearly established with respect to a contribution to a decrease in cancer mortality [24-27]. However, there is no practical or effective method of detecting PC other than screening based on the PSA level.

In conclusion, PSA testing seems to be a useful screening method for detecting PC at an early stage. We recommended that all men aged 50 years or older should participate in screening by measurement of PSA.

ACKNOWLEDGMENT

We are thankful to Mr. Shuji Takiwaki (Health Evaluation and Promotion Center, Tokai University Affiliated Hospital) for excellent technical assistance in computer analysis of the examinees screened at Tokai University Hospital.

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