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Characteristics of prostate cancers found in specimens removed by radical cystoprostatectomy for bladder cancer and their relationship with serum prostate-specific antigen level

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Prostate cancer mass screening using serum prostate-specific antigen (PSA) has been conducted widely in the world. However, little is known about the true prevalence of prostate cancer in the 'normal' PSA range (4.0 ng/mL or less). The aim of the present study was to elucidate the clinicopathological features of prostate cancer occurring in men with a wide range of PSA levels. The study comprised 349 male patients who underwent radical cystoprostatectomy for bladder cancer. Patients who had had treatment for known prostate cancer were excluded. Tissue specimens were reviewed microscopically. Ninety-one patients (26.1%) were found to have prostate cancer, and 68 (74.7%) of these 91 cancers were considered to be clinically significant. Both increasing patient age and PSA level were significantly correlated with an increased incidence of both all and significant prostate cancers. Sixty-five (21.9%) among 297 patients with PSA < 4.0 ng/mL had prostate cancer, and 45 (69.2%) of the 65 cancers were significant cancers. Eighteen patients had prostate cancers 0.5 mL or more in volume. Among the 18 patients, the PSA level was 4 ng/mL or more in 11, and 3 ng/mL or more in 15. Our study shows that prostate cancer is a common finding in radical cystoprostatectomy specimens excised because of bladder cancers, and a significant proportion of these cancers are clinically significant. PSA still appears to be a useful screening tool for detecting prostate cancers with significant volume. (*Cancer Sci* 2009; 100: 1880–1884)

Prostate cancer is one of the leading causes of mortality and morbidity in developed countries.[1] Screening of serum PSA followed by systematic prostate biopsy has enabled detection of prostate cancer at an earlier stage,[2] although it is still debatable whether mass screening using PSA contributes significantly to reduction in mortality from prostate cancer.[3]

Historically, 4.0 ng/mL PSA has been used as the threshold to prompt prostate biopsy. Although it is known that prostate cancers do exist even in the low PSA range (4.0 ng/mL or less),[4] until recently little was known about the true prevalence of prostate cancer in the low PSA range because most men in this category do not undergo prostate biopsy.[5] In 2004, Thompson *et al.* reported data from the PCPT showing that biopsy-detectable prostate cancer is not rare among men with a low PSA level (4.0 ng/mL or less).[6] This result provoked a discussion about the optimal threshold of PSA for recommending biopsy, although no definitive agreement has been reached so far.[7,8] Although the PCPT demonstrated the prevalence of biopsy-detectable prostate cancer in the low PSA range, there is still a notable lack of data based on thorough histological evaluation of the whole prostate in relation to PSA level in a large general population.

It is possible to microscopically examine the whole prostate of autopsied individuals in whom prostate cancer had not been suspected before death.[9] Although most latent prostate cancers observed in autopsy cases are small lesions, their histology is not different from clinical cancers, and they may be merely in the early phase of progression.[10,11] Usually, however, PSA levels are not available in autopsy cases.

Radical cystoprostatectomy (RCP) is a gold-standard treatment for invasive bladder cancer.[12] Even though some researchers have reported an epidemiological association between bladder cancer and prostate cancer,[13] the specimen obtained from this operation represents a fairly random sample of whole prostate tissue from asymptomatic men. Several studies have examined the incidence and histopathological characteristics of prostate cancer found incidentally in RCP specimens.[14–18] They showed that incidental prostate cancer is not rare in RCP specimens (incidence, 4–60%).[14–18] However, only a few of them examined its relationship with PSA value.[15–18]

In order to elucidate the incidence and histopathological features of prostate cancers occurring in men with a wide range of PSA levels, we reviewed 349 whole prostate tissues in RCP specimens excised because of bladder cancer in Japanese men.

Patients and Methods

Medical records of 354 consecutive men who underwent RCP for bladder cancer at the National Cancer Center Hospital between July 1995 and April 2008 were reviewed retrospectively. The study was approved by the institutional review board.

Three men were excluded from the study because they had undergone pelvic irradiation for bladder cancer before RCP. Two were also excluded because they had been diagnosed as having prostate cancer and treated with androgen ablation and/or radiation therapy before RCP. Thus, 349 men were included in the present study.

A routine pathological examination was conducted on all RCP specimens by sectioning the prostate and bladder every 5 mm. A single pathologist (YK) reviewed the specimens microscopically. Each prostate cancer was staged and graded based on the 2002 International Union Against Cancer (UICC) TNM system[19] and 2005 modified International Society of Urological Pathology (ISUP) Gleason grading system.[20] Tumor volume was calculated using the formula:

$$\text{volume} = (\text{width} \times \text{height} \times \text{length}) \times \pi/6 \times 1.5,$$

in which length is calculated from 0.5 cm multiplied by the number of slices containing tumors and 1.5 is a tissue shrinkage factor.[21]

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Table 1. Status and pathology of prostate biopsy and prostate-specific antigen (PSA) levels before radical cystoprostatectomy (RCP) in the 349 patients

PSA	Prostate biopsy before RCP		
	Yes		No biopsy
	Prostate cancer proved	Benign prostatic tissue	
<4 ng/mL	1	0	296
≥4 ng/mL	3	2	44
Unknown	0	0	3

Table 2. Characteristics of prostate cancers found in radical cystoprostatectomy specimens

Characteristic	Patients	
	n	%
Gleason score		
6 or less	24	26.4
7 (3 + 4)	54	59.3
7 (4 + 3)	9	9.9
8–10	4	4.4
pT stage		
pT2	85	93.4
pT3a	3	3.3
pT3b	1	1.1
pT4	2	2.2
Lymph node status		
pN0	89	97.8
pN1	1	1.1
pN2	1	1.1
Surgical margin status		
Not involved by tumor	87	95.6
Involved by tumor	4	4.4
Perineural invasion		
Negative	69	75.8
Positive	22	24.2

The serum PSA level was determined routinely before RCP at the outpatient clinic. Measurement of PSA levels was carried out using the Delfia-PSA assay (Pharmacia Diagnostics Co., Tokyo, Japan) until September 1997, the Lumipulse PSA assay (Fujirebio, Tokyo, Japan) until July 2004, and the Lumipulse PSA-N assay (Fujirebio) thereafter.

Correlations of clinicopathological parameters between groups were analyzed by Mann–Whitney *U*-test or Kruskal–Wallis test. Differences with *P*-values < 0.05 were considered significant.

Results

The median patient age was 65 years (range, 27–89 years). Preoperative PSA levels were not evaluated in 3 of the 349 men. The median preoperative PSA level was 1.28 ng/mL (range, 0.03–20.603 ng/mL) for the 346 patients.

In 6 of the 349 patients, prostate biopsy had been carried out before RCP. The presence or absence of prostate biopsy, pathology of the biopsy specimen, and serum PSA levels in the 349 patients are summarized in Table 1.

Ninety-one patients (26.1%) were found to have prostate cancer. Of these, four (1.1%) had been preoperatively diagnosed as having prostate cancer by needle biopsy, but had not been treated before RCP. Eighty-seven (24.9%) were found to have incidental prostate cancer.

The pathological features of these 91 prostate cancers are shown in Table 2. The distribution of the prostate cancer volumes

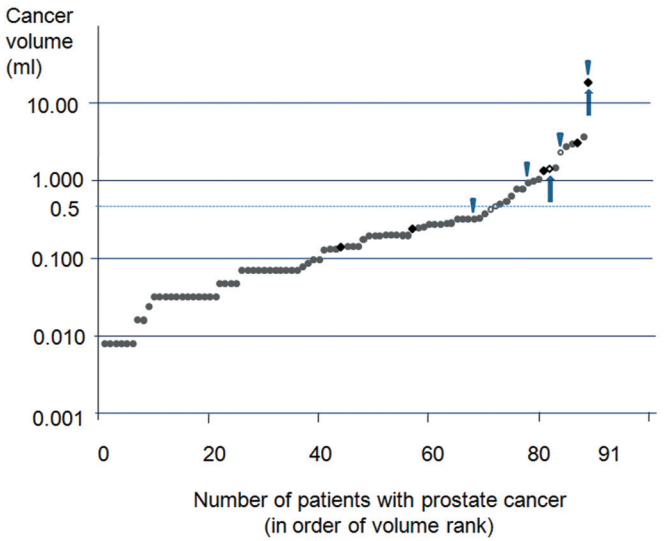
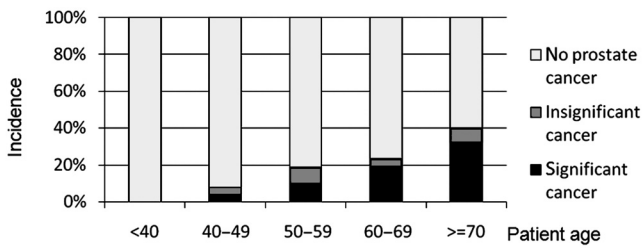


Fig. 1. Volume distribution of prostate cancers. All 91 prostate cancers are plotted in order of volume rank. Each circle and square indicates one prostate cancer. Squares indicate pT3 or pT4 cancers. Clear circles and squares indicate cancers diagnosed by biopsy before cystoprostatectomy. Arrowheads indicate cancers with a Gleason score of 8 or more. Arrows indicate cancers with lymph node metastasis.



	<40	40–49	50–59	60–69	>=70
Number of patients	6	25	80	128	110
All prostate cancer	0	2	15	30	44
	0%	8.0%	18.8%	23.4%	40%
Significant cancer	0	1	8	24	35
	0%	4.0%	10.0%	18.8%	31.8%

Fig. 2. Incidence of prostate cancer in each age group. The definition of significant cancer is given in the Results section.

is shown in Figure 1. Larger cancers were more likely to have a higher Gleason score and to have lymph node metastasis (Fig. 1). As for the relationship between cancer volume and pT stage, even small cancers could be at high pT stage: a cancer 0.23 mL in volume showed extracapsular extension (pT3a). A cancer 0.13 mL in volume arose in the prostatic base and invaded to the bladder neck (pT4).

The incidence of prostate cancer increased with patient age (Fig. 2). The median age of the patients with prostate cancer was 69 years (range, 43–81 years), and was significantly higher than that of patients without prostate cancer (median, 63.5 years; range, 27–89 years) ($P < 0.0001$, Mann–Whitney *U*-test).

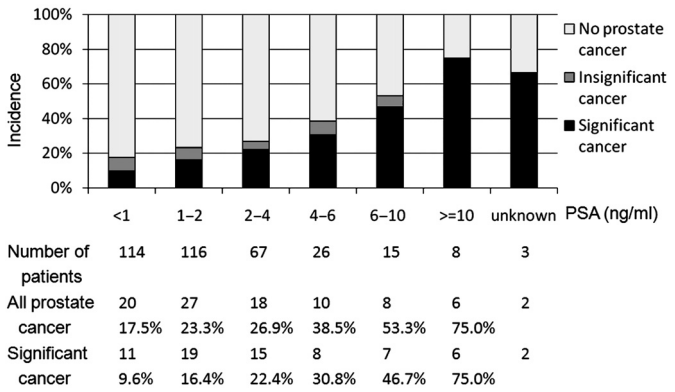
The incidence of prostate cancer increased with the PSA level (Fig. 3). The median PSA level in the patients with prostate cancer was 1.90 ng/mL (range, 0.26–20.60) and was significantly higher than in those without prostate cancer (median 1.20 ng/mL, range 0.03–13.27 ng/mL) ($P < 0.0001$, Mann–Whitney *U*-test).

Prostate cancer was considered clinically significant if any of the following criteria were present: total tumor volume ≥ 0.5 mL,

Table 3. Relationship between prostate cancer and patient age

Prostate cancer	No. patients	Median age (years)	*P*-value			
No prostate cancer	258	63.5 (range 27–89)	$P < 0.0001$*			
Prostate cancer	91	69 (range 43–81)		$P = 0.2340$*	$P < 0.0001$†	$P < 0.0001$*
Insignificant	23	67 (range 43–78)				
Significant	68	70 (range 46–81)		$P = 0.1216$*		

*Mann–Whitney *U*-test, †Kruskal–Wallis test.



	<1	1–2	2–4	4–6	6–10	>=10	unknown
Number of patients	114	116	67	26	15	8	3
All prostate cancer	20	27	18	10	8	6	2
	17.5%	23.3%	26.9%	38.5%	53.3%	75.0%	
Significant cancer	11	19	15	8	7	6	2
	9.6%	16.4%	22.4%	30.8%	46.7%	75.0%	

Fig. 3. Incidence of prostate cancer in each prostate-specific antigen (PSA) range. Definition of significant cancer is given in the Results section.

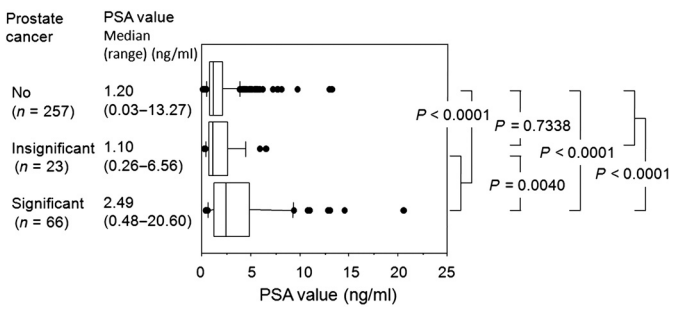


Fig. 4. Relationship between prostate cancer and prostate-specific antigen (PSA) value. The boxes show a range of 25–75 percentiles, and the whiskers a range of 10–90 percentiles. The vertical bars in each box indicate median values. Correlation was calculated using the Mann–Whitney *U*-test.

Gleason grade ≥ 4, ECE, SVI, or lymph node metastasis. Sixty-eight patients (74.7%) had significant prostate cancer. The reasons for designating these cancers as 'significant' were: tumor volume ≥ 0.5 mL in 18 patients (19.8%), Gleason grade ≥ 4 in 67 patients (73.6%), ECE in five patients (5.5%), SVI in one patient (1.1%), and lymph node metastasis in two patients (2.2%).

The incidence of significant prostate cancer increased with patient age (Fig. 2). The median age of the patients with significant prostate cancer was 70 years (range, 46–81 years), and was significantly higher than that of patients without significant prostate cancer (median, 64 years; range, 27–89 years) ($P < 0.0001$, Mann–Whitney *U*-test) (Table 3).

The incidence of significant prostate cancer increased with the PSA level (Fig. 3). Figure 4 shows the distribution of PSA levels in the patients with significant, insignificant, or no prostate cancer. The median PSA level in the patients with significant prostate cancer was 2.49 ng/mL (range, 0.48–20.60 years) and was significantly higher than in those with insignificant cancer (median, 1.10 ng/mL; range, 0.26–6.56 ng/mL) ($P = 0.0040$) and in those without cancer (median, 1.20 ng/mL; range 0.03–13.27 ng/mL) ($P < 0.0001$). The PSA level in the patients with insignificant prostate cancer was not significantly different from that in patients without cancer ($P = 0.7338$) (Fig. 4).

The median follow-up period was 36 months (range, 1–128 months) for the 91 patients with prostate cancer. None of the patients died of prostate cancer during follow-up. One patient, who had a preoperative PSA level of 5.0 ng/mL and a Gleason grade 4 + 3 prostate cancer 2.96 mL in volume, developed biochemical recurrence (PSA recurrence; PSA > 0.2 ng/mL) at 36 months after surgery without any detectable mass lesion. His serum PSA level was 0.583 ng/mL, and no additional therapy has yet been started at 42 months of follow-up.

Discussion

The incidence of prostate cancer varies among races; East Asians have a lower cumulative incidence than white and black people in the USA and Europe.[22] However, the incidence of latent prostate cancer does not differ between Japanese and white and black people in the USA.[9] Latent cancer is not different from clinical cancer in terms of histology.[10,11] The proportion of Japanese men who undergo PSA screening remains at only 5%,[23] whereas 75% of men aged 50 years or older have had a PSA test in the USA.[24] In Japan, however, the morbidity and mortality of prostate cancer have been increasing,[22] and its incidence will increase further as more men undergo PSA mass screening. Our study shows that the incidence of prostate cancer in RCP specimens from Japanese men is consistent with previous reports from the USA and Western Europe,[14–18] and similar to the reported incidences (22.5–34.6%) in Japanese autopsy cases.[9]

With regard to the age distribution of prostate cancer, Ashley showed that there is a linear relationship between the frequency of prostate cancer and age when plotted double logarithmically, and that its slope is 3.[25] In other words, the age-specific incidence of prostate cancer increases approximately with the third power of age.[25] Our present data are consistent with Ashley's classic paper (Fig. 5). Although Ashley considered that the development of prostate cancer requires three (epi)genetic events, based on the Armitage and Doll multistage carcinogenesis model,[26] our data should not be interpreted so simply; the number of (epi)genetic events required for prostate carcinogenesis cannot be determined solely on the basis of incidence data. However, we were able to confirm that prostate carcinogenesis is highly age dependent. Moreover, when we plotted the incidence of significant cancer on the same graph, the plot was linear with a slope of 4 (Fig. 5), indicating that progression to significant prostate cancer requires additional (epi)genetic events.

The PCPT revealed that a considerable proportion of men with low PSA values have prostate cancer.[6] Consequently, it has been suggested that the 'normal' PSA threshold should be discarded.[8] Moreover, there has been an argument that the significance of PSA as a tumor marker has been lost, and that PSA is better regarded as a marker of benign prostatic hyperplasia.[27] Thus, the significance of PSA in screening and prognostication

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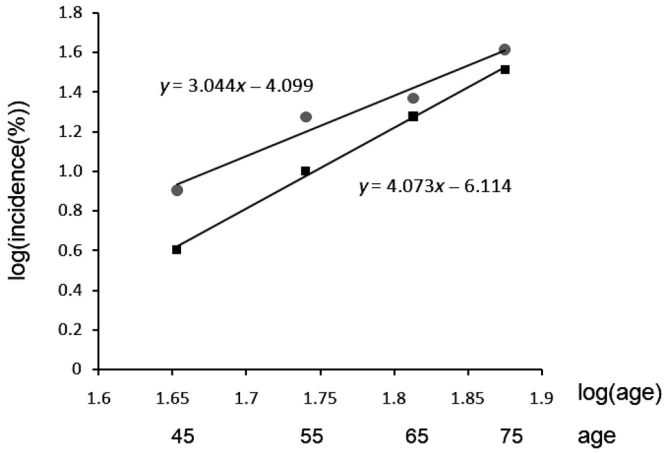

Fig. 5. Incidence of all (circles) and significant (squares) prostate cancers in every decade of patient age presented as a double logarithmic graph. Approximate lines are shown.

has recently been questioned. However, our present study indicates that increasing PSA levels are certainly associated with a higher incidence of all and significant prostate cancers. For example, the incidence of prostate cancer in patients with a PSA level ≥3 ng/mL (35/74, 47.3%) was significantly higher than in patients with a PSA level <3 ng/mL PSA (54/272, 19.9%) ($P < 0.0001$, χ^2-test). Thus, our data suggest that PSA would still be a useful screening tool for prostate cancer, at least in Japan where PSA screening is less prevalent than in Western countries.

In our study 73.5% of 'significant' cancers were small (less than 0.5 mL). Haas *et al*. reported that only 11% of cancers with a volume of less than 0.5 mL, which was estimated by computerized planimetry using an image analysis program, were detectable by 12-core biopsy in autopsy cases.[28] Therefore, most of the small 'significant' cancers in the present study would not have been detectable with current biopsy techniques. However, it is unlikely that all of these small 'significant' cancers need to be detected at such an early stage: McNeal reported that the probability of metastasis is correlated with cancer volume and grade.[11] In our present cohort of prostate cancers, we observed that most cancers with a Gleason score of ≥8 or with nodal metastasis had a volume of 0.5 mL or more (Fig. 1). Overlooking small 'significant' cancers would not compromise prognosis if patients were undergoing periodic PSA screening.

Eighteen of our patients had prostate cancers of 0.5 mL or more, which corresponds to a tumor approximately 1.0 cm in diameter. If PSA = 3.0 ng/mL were used as a threshold for recommending prostate biopsy, then 15 men with prostate cancers of 0.5 mL or more would have been included (sensitivity, 15/18 = 83.3%; specificity, 269/328 = 82.0%; positive predictive value, 15/74 = 20.3%). If PSA = 4.0 ng/mL were applied as a threshold, then an additional four men with prostate cancers of 0.5 mL or more would have been missed, resulting in lower sensitivity (11/18 = 61.1%). In addition, prostate biopsy does not always guarantee detection of all cancers with a volume of 0.5 mL or more. The threshold PSA level for prompting prostate biopsy needs to be determined carefully bearing these issues in mind.

Schröder *et al*. have reported that men with a PSA level of 3.0 ng/mL or less do not require immediate biopsy:[29] according to their analysis of data from the European Randomized Screening for Prostate Cancer Trial, which adopted 3.0 ng/mL PSA as a threshold to prompt biopsy, only six deaths from prostate cancer might have been prevented if all 15 773 eligible men with a PSA level of 3.0 ng/mL or less had undergone biopsy.

In summary, prostate cancer is a common finding in RCP specimens, with a significant proportion having the characteristics of clinically significant prostate cancer. Increasing patient age and PSA value are associated with a high incidence of all and significant prostate cancers, and PSA still appears to be a useful tool for prostate cancer screening

Disclosure Statement

The authors have no conflict of interest.

Abbreviations

ECE	extracapsular extension
PCPT	the Prostate Cancer Prevention Trial
PSA	prostate-specific antigen
RCP	radical cystoprostatectomy
SVI	seminal vesicle invasion

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