

Regional difference in cancer detection rate in prostate cancer screening by a local municipality in Japan

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Purpose: We conducted the present retrospective study to elucidate regional differences in the quality of secondary screening in the prostate cancer (PCA) screening program by a local municipality in Japan.

Methods: Of 115,881 men who attended the PCA screening in 36 municipalities between 2001 and 2011, a total of 6,099 men consulted hospitals for secondary screening. The cancer detection rate (CDR) at the secondary screening was calculated, and municipalities were classified into three CDR groups according to the age-adjusted observed-to-expected ratios of CDR. Of the secondary screening facilities, hospitals in Ibaraki Prefecture screening less than 100 patients were classified as group I facilities and the others as group II facilities.

Results: Overall, 2,320 of 6,099 secondary screening patients underwent prostate biopsy, and 1,073 men were diagnosed with PCA. The overall CDR at the secondary screening was 17.6%, but it varied from 5.6% to 34.4% among municipalities. Although there were no significant differences in age and prostate-specific antigen (PSA) distribution among the three CDR groups, a significantly higher rate of patients in low CDR municipalities visited group I facilities. Both biopsy rates and CDRs of secondary screening at group II facilities were significantly higher than those of group I facilities ($P=0.0001$). Multivariate analysis showed that the secondary screening at group II facilities as well as age and PSA levels were independent contributing factors for PCA detection.

Conclusions: CDRs at secondary screening varied widely among municipalities in Ibaraki Prefecture. Variation in CDRs was associated with biopsy rates.

Keywords: Prostate neoplasms, Prostate-specific antigen, Early detection of cancer

INTRODUCTION

Prostate cancer (PCA) is one of the common malignancies in men. The number of PCA patients increasing, and PCA is expected to become the second most frequent male cancer in Japan. Further, the PCA mortality rate will increase by 2.8 folds in 2020 compared to 2000 [1]. This increase of prevalence rate is affected by various factors including age of the population,

food, genetic factors, and also screening systems using prostate-specific antigen (PSA). PCA was generally identified by metastatic symptoms before the PSA era, but the introduction of PSA made it possible to identify PCA in the early stages.

Generally, prevention and early detection reduce the mortality rate of malignancies. For this reason, national population-based screening systems have been established in Japan for five major malignancies including lung, stomach, breast,

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colon, and cervical cancer. PSA-based screening systems for PCA have not been established by the Japanese government, but mostly administered by municipal governments since the 1990s. The Japanese Urological Association (JUA) recommends PSA-based screening for men over 50 years old, and also further examinations for patients with more than 4 ng/mL or age-adjusted cut off levels of PSA to assess the presence of PCAs [2]. Further examinations including digital rectal examinations, transrectal ultrasonography, blood examinations, magnetic resonance imaging, and/or prostate biopsy are performed as secondary screening. The definitive diagnosis of PCA is made by prostate biopsy, although the actual indication for a biopsy largely depends on decision-making practices at each facility.

The cancer detection rate (CDR) is an important indicator to evaluate screening systems for malignancies. CDR of PSA-based screening is known to be higher than those of national screening systems for the other five major cancers. According to a survey by the Japan Cancer Society, the CDR of PCA screening was 0.5% in 2011, whereas those of the other five cancer screenings were 0.04% to 0.22%. However, large regional differences in the CDRs of PCA screening were reported; the 2005 annual report of the Japanese Foundation for Prostate Research (JFPR) revealed that the CDR among men attending a primary screening varied from 0.0% to 5.1% in 218 municipalities throughout Japan [3]. Multiple factors, including the age distribution of the target population, exposure rates of PSA screening, rate of persons receiving secondary screening, quality of secondary screening, and others might be responsible for the variability. Comprehensive analysis of these factors might reveal strategies to improve the CDR, but this type of information is limited in Japan. Improvement of CDR is considered to be a common issue in most of Asian countries, where PSA exposure rates are very lower than Western countries [4]. In the present study, we extensively analyzed factors contributing to regional differences in CDRs at the secondary screening using the practice-based, retrospective data of 115,881 men who participated in PSA-based screening programs of Ibaraki Prefecture during the past 10 years. Ibaraki Prefecture is located about 100 km from Tokyo. To our knowledge, this is the first study to examine factors responsible for regional differences in CDRs of PCA screening programs by municipal governments in Japan.

MATERIALS AND METHODS

1. PSA-based screening program in Ibaraki Prefecture

PSA screening was started in Ibaraki Prefecture in 1999, and 36 of 44 municipalities in Ibaraki Prefecture have participated

in the PSA-based screening program. In the first screening, the serum PSA level alone with a cut off of 4.0 ng/mL was used, and notifications for further examinations were mailed to participants by the Ibaraki Health Service Association (IHSA). When the participants were referred to hospital or clinics for secondary screening, each facility sent the results of further examinations to IHSA using the screening report form. The available information from the screening report including examination date, patient age, name of the facility, PSA levels at secondary screenings, and the results of a prostate biopsy if performed. The percentage of individuals referred for secondary screening and CDR were aggregated annually for each municipality by IHSA. We obtained permission of IHSA committee for use of anonymised data on PCA screening in the present study.

2. Patients and facilities

Because the aggregate screening data is available from 2001, we analyzed the results of 115,881 men who attended a PSA-based screening for the first time between 2001 and 2011. During this period, as a result of municipal mergers, 84 municipalities in Ibaraki Prefecture were integrated into 44 municipalities. Therefore, we adjusted the data of each municipality according to the consequence of these municipal mergers.

In the present study, we excluded men who had previously attended the PSA-based screening program of Ibaraki Prefecture. Among 115,881 men, 8,473 men (7.3%) had a serum PSA level higher than 4.0 ng/mL at the first screening, and finally a total of 6,099 (72.0%) received the secondary screening. The profiles of these 6,099 patients are presented in Table 1. During the study period, a total of 376 hospitals or clinics conducted the secondary screening. Of them, 299 facilities were located in Ibaraki Prefecture and the remaining 77 facilities were located outside of Ibaraki Prefecture. We divided these facilities into two groups according to number of patients screened during the study period. The hospitals or clinics with less than 100 patients in 10 years were classified as group I facilities. Those with 100 or more patients and those located outside Ibaraki Prefecture were classified as group II facilities. Thus, 240 facilities and 136 facilities were classified as group I and group II facilities, respectively.

3. Statistical analysis

CDR at secondary screening, the rates of prostate biopsies performed and positive biopsy rates were calculated using the following equations:

$$\text{CDR at secondary screening} = \frac{\text{number of PCA patients}}{\text{number of patients who received secondary screening}}$$

Table 1. Participants profile in secondary screening

Variable	Value
No. of municipality	36
No. of secondary screenees	6,099
Biopsied cases, n (%)	2,320 (38.0)
No. of prostate cancer	1,073
Positive biopsy proportion	46.3%
CDR in secondary screening	17.6%
Distribution of age, n (%)	
≤59	440 (7.2)
60–69	2,631 (43.1)
70–79	2,564 (42.0)
≥80	464 (7.6)
Distribution of PSA, n (%)	
>4, ≤6	3,009 (49.3)
>6, ≤10	1,733 (28.4)
>10, ≤20	864 (14.2)
>20, ≤50	333 (5.5)
>50	160 (2.6)
Secondary screenees, n (%)	
Group I facilities ^{a)}	2,017 (33.1)
Group II facilities ^{b)}	4,080 (66.9)

CDR, cancer detection rate; PSA, prostate-specific antigen.

^{a)}Hospitals or clinics in Ibaraki prefecture with less than 100 patients.

^{b)}Hospitals or clinics with 100 or more patients in Ibaraki prefecture, and those located outside Ibaraki prefecture.

Prostate biopsy rate = number of patients who underwent prostate biopsy/number of patients who received secondary screening

Positive biopsy rate = number of PCA patients/number of patients who underwent prostate biopsy

The age-adjusted observed-expected (O/E) ratio of PCA patients in each municipality was calculated by the number of screening detected PCA patients in the municipality divided by its expected number. The expected number of PCA patients was calculated by applying the age-specific CDRs in Ibaraki Prefecture to the age-specific populations in each municipality. The age-specific CDRs in Ibaraki Prefecture was calculated from accumulated PCA screening data between 2001 and 2011. We classified 36 municipalities into three regions (high, moderate, low) by tertiles of the OER.

Differences in the factors related to CDRs at secondary screening (age, serum PSA level, type of facility) were examined by a simple logistic regression (Table 2). Differences in CDR, biopsy rate, and positive biopsy rate between facilities were examined by a chi-square test. Multivariate analyses using a logistic regression model were performed to examine the contributing factors associated with cancer detection (Table 2). *P*-values of less than 0.05 were considered statistically significant. All statistical analyses were performed using the soft-

Table 2. The factors related with cancer detection rates at secondary screening

Variable	OR (95% CI)	<i>P</i> -value
Age (yr)		<0.001
<70	1	
≥70	1.28 (1.11–1.47)	
Serum PSA level (ng/mL)		<0.001
4–6	1	
≥6	5.79 (4.90–6.86)	
Facilities		<0.001
Group I	1	
Group II	2.14 (1.82–2.54)	

OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen.

ware package JMP ver. 10.0.2 (SAS Institute, Cary, NC, USA).

RESULTS

Among 6,099 men who received the secondary screening, a total of 2,320 (38.0%) underwent prostate biopsy, and 1,073 men were finally diagnosed with PCA (Table 1). The CDR of all participants in the secondary screening was 17.6%. When CDRs were calculated by municipality, large differences in CDRs were noted: they varied from 5.6% to 35.0%. Even when CDRs in each municipality were adjusted by age-population, the age-adjusted O/E ratios of PCA patients varied from 0.39 to 2.40, as shown in Fig. 1.

To examine the possible factors contributing to the difference in CDRs, 36 municipalities were divided into three groups according to their O/E ratios. Thus, 14, 11, and 11 municipalities were classified as high, moderate, and low CDR groups (Fig. 1), and their CDRs were 22.8%, 17.0%, and 12.8%, respectively. Among the three groups divided by CDR, there was no significant difference in the distribution of age and PSA (Fig. 2). On the other hand, more patients belonging to the moderate and low CDR groups rather than the high CDR group tended to visit group I facilities (*P*=0.05 and *P*=0.001, respectively)

Next, we compared qualities of secondary screening between groups I and II facilities. As shown in Fig. 3A, the CDR of group II facilities was significantly higher than that of group I facilities in total (21.0% and 10.7%, respectively; *P*=0.0001). When participants were divided into high, moderate, and low CDR groups, similar significant differences in CDRs between groups I and II facilities were observed in all three CDR groups (Fig. 3). The rates of prostate biopsies were significantly different between groups I and II facilities, although there were no significant differences in positive biopsy rates. Multivariate analysis demonstrated that group I/II facilities, as well as age and PSA levels, were independent factors for CDR

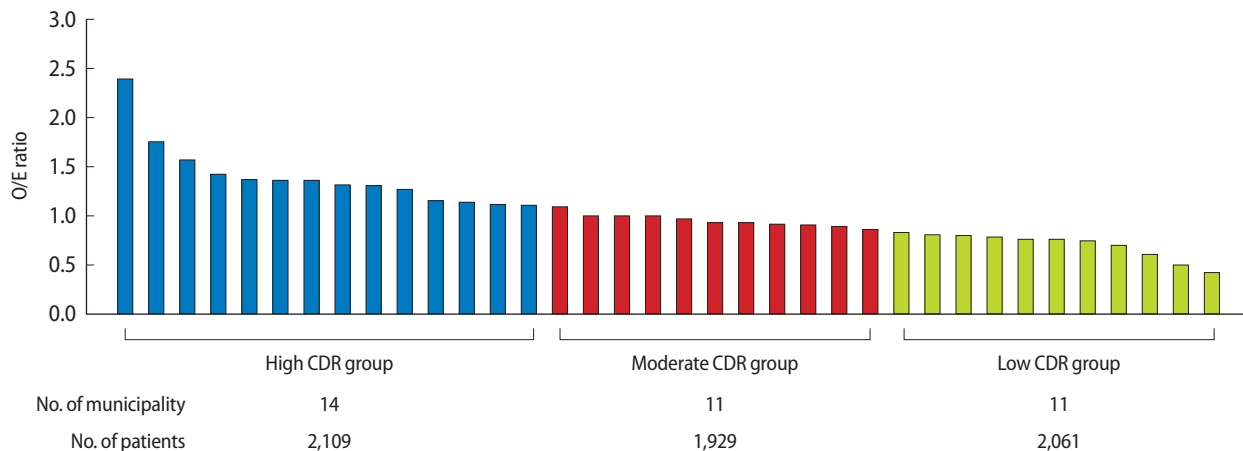


Fig. 1. The observed/expected number of prostate cancer (PCA) patients who attended secondary screening in each municipality. Thirty-six municipalities were divided to three groups according to the observed-to-expected (O/E) ratios of numbers of PCA. CDR, cancer detection rate.

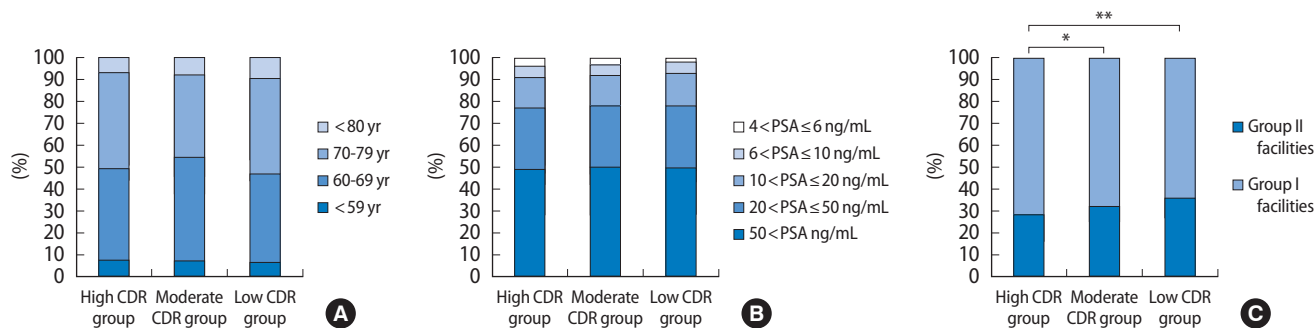


Fig. 2. Distribution of patient age (A), serum prostate-specific antigen (PSA) levels (B), and referral facilities (C) among three municipality groups divided by cancer detection rate (CDR). Significant differences in referral facility among the three groups were noted (C). There was no significant difference in patient age (A) and serum PSA level (B). * $P < 0.05$. ** $P < 0.01$.

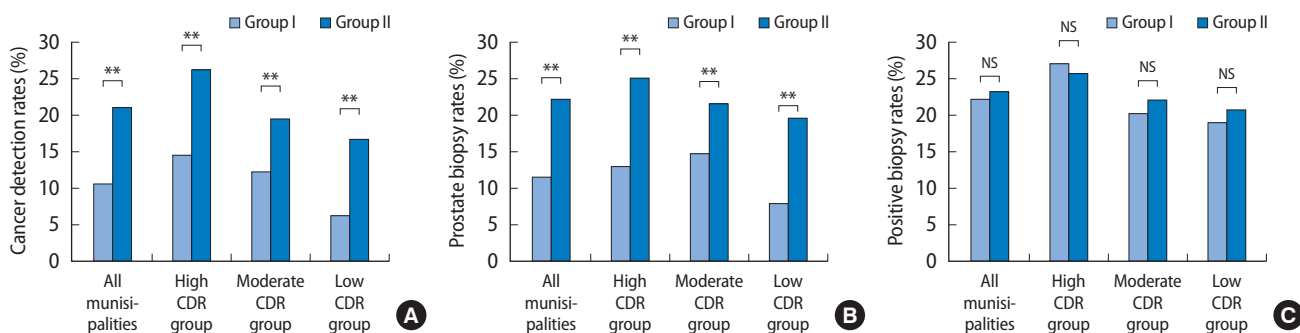


Fig. 3. Differences in cancer detection rate (CDR) (A), biopsy rate (B), and positive biopsy rate (C) between groups I and II facilities. Significant differences in CDR (A) and biopsy rate (B) were noted between groups I and II facilities. There was no significant difference in positive biopsy rate (C). NS, not significant. ** $P < 0.01$.

in secondary screening of participants with high PSA levels, as shown in Table 2. To elucidate why the CDRs in groups I and II facilities were different, participants were stratified by PSA levels (Fig. 4). Interestingly, the CDRs of group II facilities increased according to PSA levels in a similar pattern in

all three municipality groups, whereas the CDRs in the group I facilities were significantly lower than the group II facilities for participants with more than 20 ng/mL PSA in moderate and low CDR municipality groups. In high CDR municipality groups, the CDRs for participants with 10–20 ng/mL of PSA

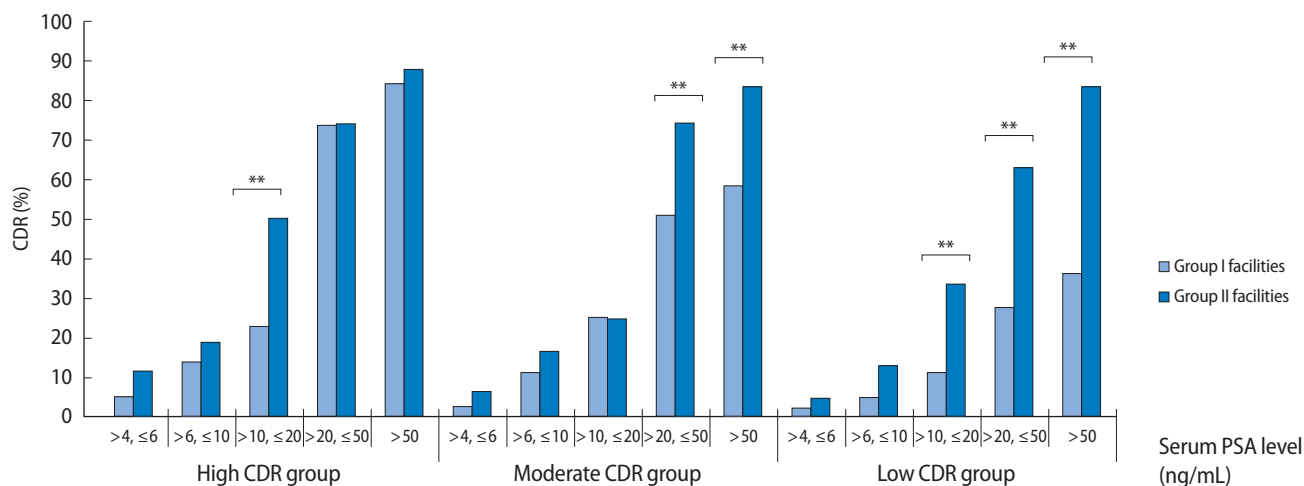


Fig. 4. Difference in cancer detection rate (CDR) between groups I and II facilities according to serum prostate-specific antigen (PSA) levels. ** $P < 0.01$.

were significantly different between groups I and II facilities.

DISCUSSION

In the present study, we analyzed the results of 6,099 men who underwent secondary screening in the practice-based PCA screening program of Ibaraki Prefecture and demonstrated that CDRs at the secondary screening varied largely among municipalities from 5.6% to 35.0%. These variations were also observed when the age distributions were adjusted. Similarly, the 2005 annual report of JFPR revealed that CDRs at the primary screening varied from 0% to 5.1% among 218 municipalities over Japan [3]. These data indicate that this variation of CDR at secondary screening is an important issue for PCA screening not only in Ibaraki Prefecture but also all over Japan. Generally, CDRs at the secondary screening could be affected by several factors including age distribution, PSA distribution, and the rate of prostate biopsies performed. To elucidate the factors contributing to the wide variations of CDR might provide crucial information for improving CDR at secondary screening.

In the present study, we demonstrated several important findings. First, significant differences in CDRs were observed between facilities at the secondary screening. The CDRs in group I facilities, which had accumulated fewer than 100 participants in 10 years, were approximately half of those in group II facility. This tendency was observed in all three municipality groups. Furthermore, the multivariate analysis demonstrated a significant association between facility groups at secondary screening and CDRs, indicating that it was an independent predicting factor for PCA detection as well as age and serum PSA levels.

The second important finding was that group II facilities demonstrated a significantly higher rate of prostate biopsy rather than group I facilities in accordance with CDRs between facility groups, but a similar rate of positive biopsies. In the European Randomized Study of Screening for Prostate Cancer (ERSPC), Otto et al. [5] revealed that differences in protocol rather than a true underlying incidence of PCA could contribute to the high variation of CDR among European countries, although it was not restricted to biopsy rate. These observations suggested that the variations in CDRs were associated with biopsy rates.

Several factors have been reported to be related to the rates of prostate biopsy for patients with high PSA. In the United States, significant variations of accessibility or compliance to PCA screening were observed among race, ethnicity, and residency. Fedewa et al. [6] reported that insurance status was strongly associated with PCA disease severity and concluded that the lack of access to services such as PSA screening might be responsible for the variations of disease severity. Also, in another large screening trial, non-Hispanic black men had significantly lower access to diagnostic care after a positive PSA screening [7]. A nationwide multicenter study in Korea revealed a significantly lower incidence of biopsy in local clinics than in general hospitals (21.6% vs. 66.2%) [8]. In Japan, where a national health insurance system is established, a disadvantage from insurance status can be almost negligible. One plausible explanation for variations in biopsy rates is that accessibility to specialized care differs after positive PSA screening. These data suggested the necessity of establishing a referral system for biopsy in the screening program.

Another possible explanation for wide variations of prostate biopsy is a more conservative attitude toward making the de-

cision for a prostate biopsy in general practice compared to an academic setting. In ERSPC, the average rate complying with a biopsy recommendation is as high as 85.6% [9]. Although not necessarily directly comparable, the overall biopsy rate at the secondary screening in the present study was limited to 38%. This biopsy rate was also somewhat lower than the JFPR data. According to the 2005 JFPR report, the overall biopsy rate of second screening participants was 51.9%. But, importantly, the JFPR report also showed a large regional difference in biopsy rates at secondary screening; it differed from 0% to 100% among municipalities. A similar difference in compliance with the biopsy recommendation was observed in an active surveillance program. The reported first biopsy rate was as high as 80% in the PRIAS study [10]. In contrast, Lee et al. [11] demonstrated a 53% compliance rate within one year in a U.S. Veterans Affairs population. Multiple factors are supposed to underlie the lower compliance in general practice, such as less patient education and poorer physician-patient communication.

The present retrospective study has several limitations. The detailed information such as procedure of informed consent, the intensity of recommendation for prostate biopsy and biopsy strategy in each facility was lacking. Those factors can directly affect CDR of each facility. In addition, unfortunately in Ibaraki Prefecture, the reliable information on regional difference in exposure rate for PSA screening was not available. If regional difference of PSA exposure rate exists, it can affect regional CDRs in PCA screening. Next, biopsy rate and CDR were estimated on screening reports from facilities where PSA-positive patients had first visited. Therefore, it is possible that some patients transferred to another hospital for further evaluation. This may result in underestimation of biopsy rate and CDR. This database does not include detailed information on patients such as comorbidity or other reasons to avoid biopsy. Finally, if patients and physicians decided to follow up a serum PSA at the first visit, follow-up data was not available in the present study. Therefore, there is a possibility that some nonbiopsied patients were finally diagnosed with PCA at further follow-up.

In conclusion, we demonstrated that CDR varied greatly among municipalities, and that the variation in CDRs was associated with biopsy rates but not a difference in target populations among municipalities in Ibaraki Prefecture. The different decisions made for prostate biopsy are considered to be responsible for the variation of biopsy rates.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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