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Original Article

Cost-effectiveness Analysis of Prostate Cancer Screening

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Abstract

To determine the optimal strategy for prostate cancer screening, the cost-effectiveness of screening was analyzed using a medical decision model. One hundred thousand asymptomatic males between the ages of 40 and 69 were modeled with and without screening. The subjects were divided into three 10-year age groups. We used a 5-year survival rate as an effectiveness point and assumed after 5 year survival free from prostate cancer. We considered three potential programs: 1) screening with digital rectal examination (DRE), 2) screening with prostate specific antigen (PSA), and 3) screening with a combination of DRE and PSA. The study was analyzed from the payer's perspective, and only direct medical costs were included.

For each of the three age groups, PSA screening was more cost-effective than either DRE screening or a combination of DRE and PSA screening. The cost-effectiveness ratio for the combination of DRE and PSA screening was 1.1-2.3 times more expensive than that of PSA screening. If the compliance rate for work-up exams is 80%, the cost-effectiveness of prostate cancer screening is approximate to that of gastric cancer screening. In conclusion, PSA screening is the most cost-effective strategy for prostate cancer screening when compared with both DRE and the combination of DRE and PSA screening. But prostate cancer screening should be carefully conducted, taking the cost-effectiveness of the different strategies and target groups into consideration.

Key words: prostate cancer, prostate cancer screening, cost-effectiveness analysis, prostate specific antigen (PSA), digital rectal examination (DRE)

INTRODUCTION

The leading cause of death in Japan is malignant neoplasms, which account for 28.5% of all deaths [1]. The mortality rate from malignant neoplasms has been increasing, and the number of deaths reached 263,022 in 1995 [1]. Although the prevalence of prostate cancer in Japan is still low compared with that of the US and Europe, the mortality rate from prostate cancer has been gradually increasing as a results of the aging population [2,3]. Deaths from prostate cancer doubled in the two decades between 1975 and 1995 [3]. Even now, deaths from prostate cancer account for 2.9% of all deaths from malignant neoplasms [1].

Although there are some uncertain factors in connection with its benefits, the demand for prostate cancer screening has been increasing along with the aging of the population because of increased fears of prostate cancer. The main strategies for prostate cancer screening are digital rectal examination (DRE), prostate specific antigen (PSA) and transrectal ultrasound (TRUS). The ability of PSA to detect prostate cancer at an early stage has raised hopes that screening might reduce the mortality rate for prostate cancer. PSA is a common strategy for prostate cancer screening, but the combination of DRE and PSA has also been conducted widely, mainly in general health check-ups [3-5]. However, prostate cancer screening has not been introduced as a general population-based screening procedure. Presently, the strategy for prostate cancer screening is selected on a case-by-case basis, depending on the purpose, target group and screening cost. The standardization of a reliable and economical screening strategy has become necessary. The objective of this study is to determine the optimal strategy for prostate cancer screening in Japan.

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METHODS

Model Structure

The cost-effectiveness of prostate cancer screening was analyzed by employing a medical decision model (Figure 1). We examined a general population cohort of males between the ages of 40 and 69 with a baseline prevalence of prostate cancer. In the present study, calculations have been restricted to only the ages of 40 to 69 years. This is the population that would most likely be the target for routine screening in the future. One hundred

thousand asymptomatic males between the ages of 40 and 69 years were modeled with and without screening. The subjects were divided into three 10-year age groups. A 5-year survival rate was used as an effectiveness point, and the chances after the 5 year survival period free from prostate cancer were estimated.

Three potential screening programs were considered: 1) screening with DRE, 2) screening with PSA, and 3) screening with a combination of DRE and PSA. Subjects in the model for no screening were assumed to visit a hospital only upon the appearance of symptoms. Each program included a single episode of screening, not a series of annual or repeated screens. Subjects with positive screening results received a work-up exam in which a diagnostic search for prostate cancer was made. The work-up exams included TRUS, a needle biopsy, and a reexamination of tumor markers[6]. The compliance rate for the work-up exams was assumed to be 100% for the baseline analysis. Cases of prostate cancer that were missed by the screening were assumed to develop symptoms leading to a hospital visit and diagnosis within a year of the screening. Data on the risk associated with the needle biopsies was not available, so this factor was not included in the models. Subjects with detected cancer received a prostatectomy, hormonal therapy and radiotherapy within five years according to their stage.

Data Used in the Model

Table 1 presents the assumptions as well as the acquired data and their sources. We estimated the prevalence rate of detected cancer using general population screening studies that utilized all available screening methods. The actual prevalence of prostate cancer was calculated on the basis of the detection rate of prostate cancer screening [4)-7)]. The sensitivity and specificity of each strategy were defined using the results of the reported study[7)]. Data on the sensitivity and specificity of the combination of DRE and PSA screening program was not available for the Japanese population. Instead, these parameters were estimated using previously reported cancer detection rates for each strategy[4) 7)]. The sensitivity and specificity of the work-up exams were assumed to be 100%, since the work-up exams consisted of a combination of several examinations, including TRUS, a needle biopsy and a reexamination of tumor makers[6)]. The baseline analysis compliance rate for the work-up exams was assumed to be 100%. The life expectancy for each age group was assumed to be the middle-aged people, and acquired from the 18th Life Table in Japan in 1995[8)]. The distribution for the stage of the detected prostate cancer and the 5-year survival rate were quoted from previous studies[4) 5) 9)] (Table 2). Based on these data[4) 5) 9)], we calculated the 5-year survival rates for prostate cancer detected by each screening program.

This study was analyzed from the payers' perspective. Spending costs included direct medical costs only. The cost estimates used in this model were based on the medical reimbursement rates reported for 1999[10)], and other studies[6) 7) 11) 12)]. Although DRE was included in the doctors' fee[10)], the cost of DRE was assumed to be $ 8.3 on the baseline analysis according to a previous report[11)]. The cost of the work-up exams included

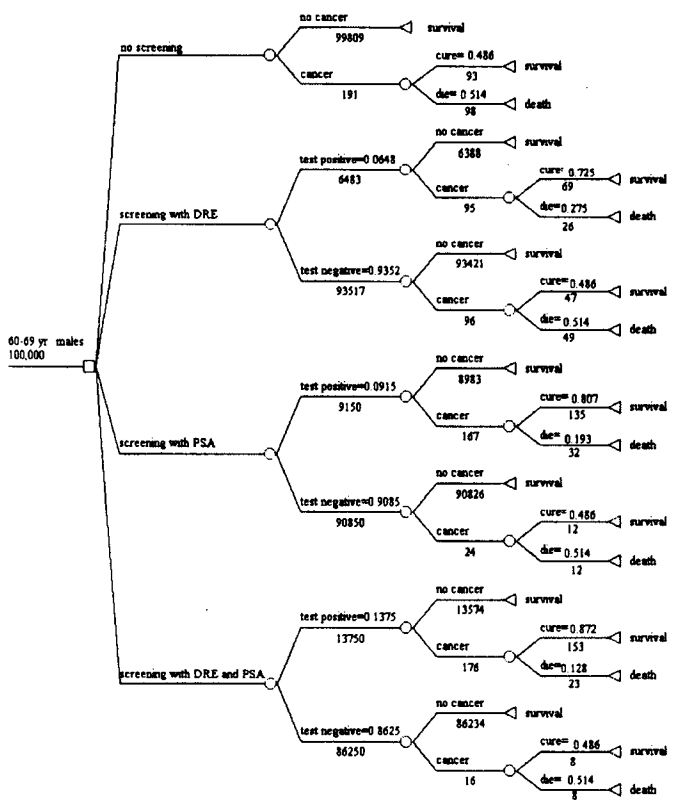

Figure 1 Decision model

Table 1 Major estimates and assumptions

		baseline value	reference
DRE sensitivity		0.500	7
specificity		0.936	7
cost (US$)		8.3	11
PSA sensitivity		0.875	7
specificity		0.910	7
cost (US$)		31.3	10
DRE+PSA sensitivity		0.919	
specificity		0.864	
cost (US$)		39.6	10, 11
work-up exams sensitivity		1.000	
specificity		1.000	
cost (US$)		245.2	6
coverage rate (%)		100	
5 yrs-survival rate			
no screening group		0.486	9
screening group DRE		0.725	4, 5, 9
	PSA	0.807	4, 5, 9
	DRE+PSA	0.872	4, 5, 9
life expectancy			
	40-49yrs (45yrs)	33.28	8
	50-59yrs (55yrs)	24.41	8
	60-69yrs (65yrs)	16.48	8
treatment cost (US$)			
	stage A/B	16,667	7
	stage C/D	50,000	7
terminal care cost (US$)		15,833	12

Table 2 Stage of Detected Cancers

strategy	distribution of detected cancers (%)				reference	5-yr survival rate
	stage A	stage B	stage C	stage D		
screening DRE	-	60.0	20.0	20.0	4, 5, 9	0.725
PSA	-	72.5	22.5	5.0	4, 5, 9	0.807
DRE+PSA	-	85.7	14.3	0.0	4, 5, 9	0.872
outpatient	18.0	22.0	18.5	41.5	9	0.486

the examination fee for TRUS and the needle biopsy as well as the cost of drugs to prevent complications[6,10]. The treatment cost was calculated using the distributions for cancer detected by screening and outpatients over a five-year period, respectively[4,7,9]. Future costs and life-year were discounted by an annual rate of 5%. The exchange rate was set at 120 yen=US $ 1 in this analysis.

RESULTS

Table 3 shows the estimated cost and effectiveness of 'no screen' and the screening programs for the 60 to 69 age group. The total cost included screening, work-up exams, treatment and terminal cost. The effectiveness was based on life-year of survival for cured cases from prostate cancer. The estimated cost and effectiveness were undiscounted in Table 3. In screening programs, although the treatment cost for prostate cancer remarkably decreased, life-year of survival for cured cases increased. Table 4 presents the estimated cost and effectiveness of the various screening programs for three age groups. The estimated cost and effectiveness were discounted at 5% in Table 4. Compared to the 'no screening' program, the life-year of survival increased for all age groups participating in the three screening programs. According to the increase of life-year of survival for cured cases, the total cost increased, too. The cost-effectiveness ratios ranged from $3,000 to $ 32,900 per incremental year of life saved with PSA screening. For the combination of DRE and PSA screening program, the cost-effectiveness ratios ranged from $3,200 to $ 75,500 per incremental year of life saved. In addition, the cost-effectiveness ratios ranged from $3,700 to $ 74,200 per incremental year of life saved with DRE screening. Although the cost-effectiveness ratio of DRE screening was approximate to PSA screening in 60-year-old males, incremental years of life saved were smaller than that of PSA screening. PSA screening was more cost-effective than both DRE and the combination of DRE and PSA screening for all age groups. The cost-effectiveness ratio for the combination of DRE and PSA screening was 1.1-2.3 times more expensive than PSA screening. In conclusion, PSA screening is the most cost-effective strategy for prostate cancer screening when compared with DRE and the combination of DRE and PSA screening.

Table 3 Estimate of cost and effectiveness (60-69 yr males)

	no screening	DRE	PSA	DRE+PSA
number of cured cases	92.8	115.7	146.5	160.6
life-years of survival for cured cases (yrs)	1,529.8	1,905.9	2,413.9	2,464.4
screening cost (1,000$)	0.0	833.3	3,125.0	3,958.3
diagnosis cost (1,000$)	46.8	1,612.9	2,249.1	3,347.7
treatment cost (1,000$)	8,555.1	7,558.4	5,897.5	4,810.0
total cost (1,000$)	8,602.0	10,004.6	11,271.6	12,143.1

*Neither 'life years' nor 'cost' were discounted

Sensitivity analyses

Sensitivity analyses were performed for central variables. Table 6 demonstrates the stability of our analysis to changes in sensitivity and specificity in a cohort of 60-year-old males. Other study reported low specificity (0.321) and high sensitivity (0.667) in DRE screening[13]. We conducted sensitivity analysis in DRE screening ranging from 0.30 to 0.90 in specificity and from 0.50 to 0.70 in sensitivity. The highest specificity with highest sensitivity for DRE screening was the most cost-effective condition. In addition, the same study reported sensitivity and specificity of PSA screening, in which sensitivity was 0.833 and specificity was 0.848[3]. We performed sensitivity analysis in both PSA and the combination of DRE and PSA screening under the assumption ranging from 0.80 to 0.95 in specificity and from 0.70 to 0.95 in sensitivity. In same specificity, the combination of DRE and PSA screening was more cost-effective than PSA screening. But, according to an increase in both sensitivity and

Table 4 Estimate of costs and effectiveness for 'no screening' and screening programs

age-group	no screening		DRE		PSA		DRE+PSA	
	life-years of survival for cures cases (yrs)	total cost (US1,000$)	life-years of survival for cures cases (yrs)	total cost (US1,000$)	life-years of survival for cures cases (yrs)	total cost (US1,000$)	life-years of survival for cures cases (yrs)	total cost (US1,000$)
40-49yrs	65.4	182.0	81.4	1,374.2	103.1	1,425.6	113.1	3,785.9
50-59yrs	288.9	1,096.6	360.0	2,396.0	455.9	3,923.7	499.8	4,949.5
60-69yrs	1,057.3	5,944.6	1,317.3	6,913.9	1,668.3	7,789.5	1,829.0	8,391.8

*Both 'life years' and 'cost' were discounted at 5%

Table 5 Incremental cost-effectiveness of prostate cancer screening

age-group	DRE		PSA		DRE+PSA	
	△years of life saved (yrs)	C/E (US1,000$years of life saved)	△years of life saved (yrs)	C/E (US1,000$years of life saved)	△years of life saved (yrs)	C/E (US1,000$years of life saved))
40-49yrs	16.1	74.2	37.8	32.9	47.7	75.5
50-59yrs	71.0	18.3	167.0	16.9	210.9	18.3
60-69yrs	260.0	3.7	611.0	3.0	771.7	3.2

combination of DRE and PSA screening yielded the largest gain in life-year of survival for cured cases in all age groups. Although the benefit of cancer treatment in terms of life-year of survival for cured cases was smaller in older males, cancer was detected more frequency in males of advancing age. Thus, screening programs produced the smallest gain in life-year of survival for cured cases in the 40 to 49 age group.

Table 5 shows the difference in years of life saved among the three screening programs and no screening for all age groups. The

Table 6 Sensitivity analysis of sensitivity and specificity in three programs

screening program	specificity	sensitivity	C/E (US1,000$/years of life saved)
DRE	0.30	0.50 ~ 0.70	45.1 ~ 31.5
	0.60	0.50 ~ 0.70	25.6 ~ 17.5
	0.90	0.50 ~ 0.70	6.1 ~ 3.6
PSA	0.80	0.70 ~ 0.95	8.3 ~ 5.3
	0.95	0.70 ~ 0.95	3.1 ~ 1.2
DRE+PSA	0.80	0.70 ~ 0.95	7.1 ~ 4.3
	0.95	0.70 ~ 0.95	2.7 ~ 1.1

Table 7 Sensitivity analyisis of variable costs

variable	cost (US$)	C/E (US1,000$/years of life saved)		
		DRE	PSA	DRE+PSA
DRE screening cost	5	2.8	3.0	2.9
	baseline	3.7	3.0	3.2
	30	9.5	3.0	5.1
PSA screening cost	10	3.7	0.6	1.3
	baseline	3.7	3.0	3.2
	50	3.7	5.1	4.9
treatnment cost	stageA/B 10,000 stageC/D 30,000	2.2	2.1	2.9
	baseline	3.7	3.0	3.2
	stageA/B 20,000 stageC/D 60,000	-1.1	-0.9	0.3
terminal cost	10,000	4.5	3.6	3.6
	baseline	3.7	3.0	3.2
	30,000	1.9	1.6	1.8

specificity of PSA, the cost-effectiveness of PSA screening was almost equal to the combination of DRE and PSA screening.

Table 7 shows the sensitivity analysis of screening, treatment and terminal cost. Concerning the PSA screening cost, PSA screening was more cost-effective than the combination of DRE and PSA screening. But, if PSA screening costs are set at $50, the cost-effectiveness of the combination of DRE and PSA screening is superior to that of PSA screening. In addition, if the screening cost of DRE is reduced, DRE screening could be the most cost-effective strategy. Considering both treatment and terminal cost, PSA screening is always more cost-effective than the combination of DRE and PSA screening.

Figure 2 shows the stability of our analysis to changes in the prevalence rate of prostate cancer. The cost-effectiveness ratios for PSA screening were superior to both DRE and the combination of DRE and PSA screening even if changes in the above prevalence rate occurred. Lastly, the effect of the compliance rate for work-up exams was determined with each screening (Figure 3). In the baseline analysis, compliance with work-up exams was set at 100%. With PSA screening, a compliance rate of over 85% was required to exceed the effect of the combination of DRE and PSA screening. Every strategy requires a high rate of compliance with work-up exams to maintain their cost-effectiveness.

DISCUSSION

In Japan, PSA screening for prostate cancer screening is rapidly becoming popular because of the simplicity of its procedure and the increasing fears of prostate cancer in the aging population. Although the incidence of prostate cancer has been gradually increasing in recent years [3) 14)], the number of deaths from prostate cancer in Japan is still lower than that of the US and Europe [2)]. Both a high incidence and a high mortality rate are firstly required to perform cancer screening. Although screenings allow cancer to be found at an earlier stage, the cost of screenings and work-up exams must also be taken into consideration. The cost and benefits of cancer screening depend on the screening strategy. To determine an optimal strategy for prostate cancer screening, a cost-effectiveness analysis of screening strategies was performed using a medical decision model.

PSA screening was found to be the most attractive screening policy for all age groups. DRE screening is a common strategy for prostate cancer screening and has been included as part of general check-ups. However, DRE screening produced a small increase in the life-year for survival for all age groups because advanced tumors account for over 40% in the cancer detected by DRE screening [4) 5)]. In our analysis, the combination of DRE and PSA screening produced a slightly smaller gain than PSA screening. The combination of DRE and PSA screening proved to be more sensitive, but the cost of the work-up exams also increased because of specificity reducing by the combination of the two strategies. Gustafsson et al. [15)] studied the cost-effectiveness of six different screening strategies except PSA only screening in a random selection of males in a defined population. In their study, TRUS screening with PSA was most cost-effective strategy, and the second was the combination of DRE and PSA screening. However, considering the low prevalence of prostate cancer, PSA screening seems to be a preferable screening strategy in Japan.

The uncertainty of our models was examined using statistical tests and sensitivity analyses. When data is modeled, a sensitivity analysis is required to assess the robustness of the conclusions of the study. A sensitivity analysis is also required for all economic evaluations [16)]. Because of lack of data for economical evaluation, data collections caused some problems in our study. We conducted sensitivity analysis for various factors. Our conclusion was supported by sensitivity analyses in various categories. However, a high compliance rate with work-up exams of over 85% is necessary to maintain the cost-effectiveness of PSA screening. In addition, a high degree of accuracy for PSA screening is also required.

In our analysis, the incremental cost-effectiveness of the combination of DRE and PSA screening was $3,200 at the age of 65. Gustafsson et al. [15)] reported that a screening strategy that included PSA as the method of examination, and DRE, if PSA was $>4 \geq$ ng/ml, resulted in a cost per cancer treatment for cure was $5,930(direct cost to $3,092). In their study, costs for screening in the different strategies are included, but not treatment costs. A Swedish study demonstrated $6,073 per cancer case treated with potentially curative therapy [17)]. On the other hand, the incremental cost-effectiveness of the combination of DRE and PSA screening has been reported in the US as $12,502 for 60-year old males [18)]. The difference of cost-effectiveness depends on the method. The US study was based on cost-utility analysis and considered the side effects of cancer treatment. We did not include quality-of-life effects in our model, but complications from prostate cancer treatment would

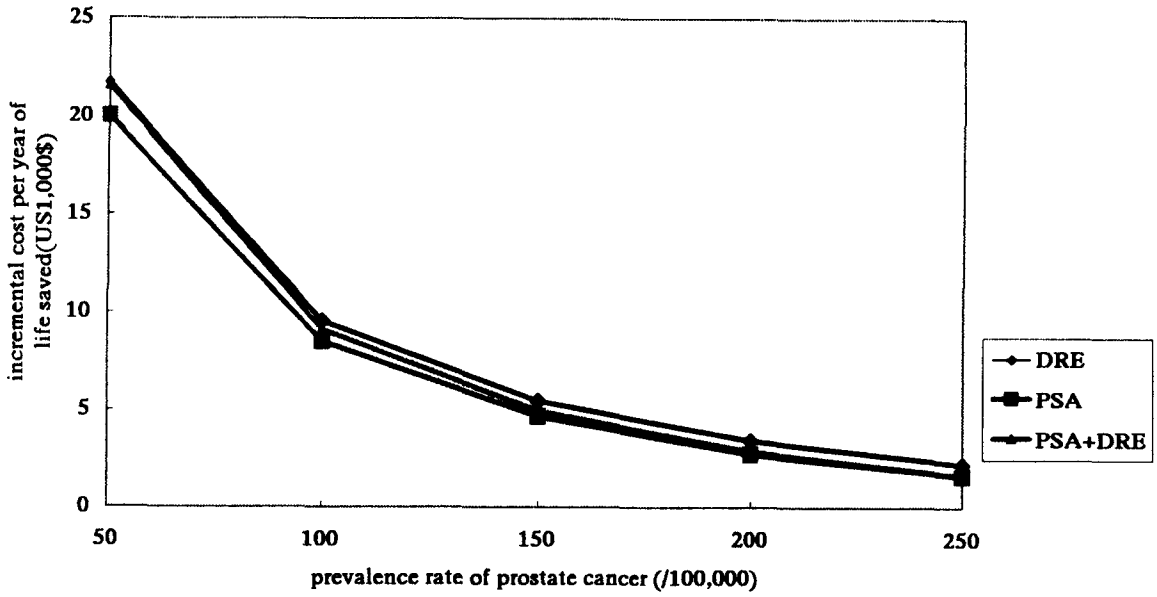

Figure 2 Sensitivity analysis of prevalence rate

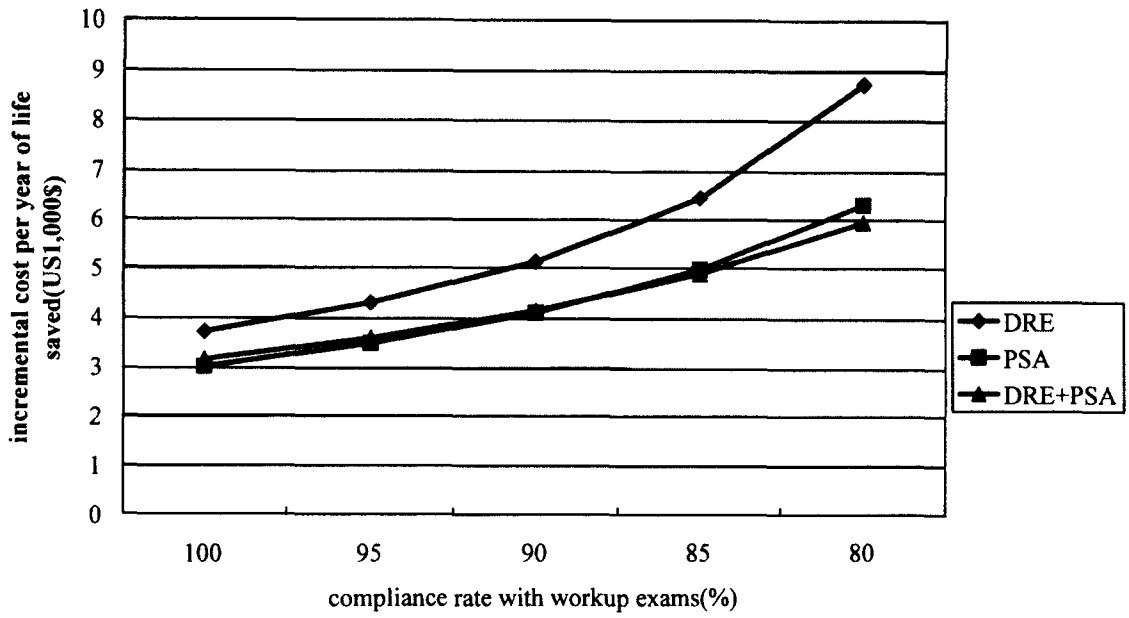

Figure 3 Sensitivity analysis of compliance rate with work-up exam

affect quality-of-life in the long-term. Complications include impotence (complete and partial), incontinence (complete and partial), obturator nerve injury, chronic cystitis and chronic proctitis. These complications could affect the cost-effectiveness of the screening programs, and a major problem with our study was an underestimation of these complications. The methods of treatment for these complications, particularly for radical prostatectomy, should be considered when evaluating the economics of prostate cancer screening.

To prevent premature death, cancer screenings for gastric and cervical cancer were started in Japan around 1960. For an approximate reason, the Health Care Law for the Aged was enacted in 1983. Since the introduction of the Health Care Law for the Aged, cancer screening has become available throughout Japan. This law provides for five cancer screenings, including gastric, uterus (uterine cervix and corpus), lung, colorectal and breast cancers. However, prostate cancer screening has not been included in this program. PSA screening is now included in many health check-ups, but a clear strategy for screening has not yet been defined[3) 4) 5)]. The cost-effectiveness ratio of DRE screening was approximate in 60-year-males, but the life-year of survival for cured cases was always less than for PSA screening. DRE screening could become more cost-effective if conditions for DRE screening are prepared. But the accuracy of DRE varies with the skill of the clinician[4) 19)]. In the general health check-up system, the combination of DRE and PSA screening is assumed to be an inefficient strategy for prostate cancer screening because most of the participants are males between the ages of 40 and 59. However, even though prostate cancer screening is less cost-effective for males in this age group, the strategy for prostate

cancer screening should be considered carefully on a clinic-by-clinic basis.

The cost-effectiveness of prostate cancer screening will play an important role in its introduction as a preventive policy. If the compliance rate for work-up exams is 80%, the cost-effectiveness of prostate cancer screening is approximate to that of gastric cancer screening[20]. However, in our study, the cost-effectiveness ratio was possibly underestimated because both the prevalence and compliance rate for work-up exams were assumed to be higher than that of the present condition. Although the target of prostate cancer screening is limited[21-23], an annual PSA screening program may decrease the prevalence of prostate cancer, and shift the distribution of detected cancers towards earlier clinical stages in screened populations[23].

Prostate cancer screening was not recommended by a US task force[24] because it could not be supported by RCT. Three randomized controlled studies for prostate cancer are ongoing,, namely, the Quebec study[25], started in 1988, the prostate, lung, colon and ovarian (PLCO) trial[26], started in 1995, and the European Randomized Study of Screening for Prostate Cancer (ERSPC)[27,28], started in 1995. Results from the last two studies are not expected before the year 2005. The Quebec RCT has reported the effects of prostate cancer screening using annual or biannual PSA tests in males over the age of 50[25]. However, in the Quebec RCT, some problems were pointed out such as randomization, compliance rate and strategy of analysis[29,30]. Recently, an International Prostate Cancer Screening Trial Evaluation Group decided to wait for the outcomes of these trials before advocating widespread population screening[31]. While the incidence of prostate cancer has been decreasing ever since the introduction of PSA screening in the US[23,32,33], the prevalence of prostate cancer is presently increasing in Japan. Our study, based on the data available in 1999, suggests the optimal strategy for prostate cancer screening in Japan. However, conclusive evidence for prostate cancer screening derived by randomized screening trials is not yet available. In view of this situation, the introduction of prostate cancer screening should be seriously evaluated with consideration given to both the benefits and the risks for target groups.

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