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Prostate cancer screening strategies with re-screening interval determined by individual baseline prostate-specific antigen values are cost-effective☆

T. Kobayashi [a,d,*], R. Goto [b], K. Ito [c], K. Mitsumori [a]

[a] *Department of Urology, Hamamatsu Rosai Hospital, Hamamatsu, Japan*
[b] *Faculty of Economics, Konan University, Kobe, Japan*
[c] *Department of Urology, Gunma University School of Medicine, Maebashi, Japan*

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Abstract

Aims: To determine whether prostate cancer screening strategies with re-screening interval determined by individual baseline prostate-specific antigen values are cost-effective.
Methods: Based on the results of an actual contemporary screening program, we established Markov decision analytic models of prostate cancer screening with personalized re-screening interval strategies using cutoff baseline PSA levels for biennial screening as well as a model of uniformly annual or biennial screening. These strategies were compared in terms of cumulative incidence of early cancer and cost-effectiveness.
Results: Early cancer detection rates were similar among all strategies. Personalized strategies were more cost-effective compared to uniform screening strategies. If all participants with negative PSA results uniformly omit annual screening, it would be more costly but less effective (dominated). Contrary, annual screening for all participants would cost too much. These results were robust throughout sensitivity analysis incorporating every assumption in the models.
Conclusions: This study adds important evidence that personalized rescreening strategies based on individual baseline PSA have advantages of cost-effectiveness against conventional uniform strategies.

Keywords: Prostate neoplasms; Mass screening; Cost-effectiveness; Prostate-specific antigen (PSA); Decision-analytic model

Introduction

On the strength of useful serum tumor marker, prostate-specific antigen (PSA), population-based prostate cancer screening programs are widely organized around the world. According to some outcome studies, the widespread use of serum PSA for prostate cancer screening has led to identification of an increasing number of asymptomatic low-stage tumors in younger men[1,2] and decrease disease-specific mortality.[3] On the other hand, however, some investigators strike a note of warning against the current popularization of prostate cancer mass screening without definitive evidence of reducing prostate cancer mortality.[4]

Once a screening program has been carried out for several years, the determination of the optimal rescreening interval becomes one of the most important issues, since longer interval without spoiling detection performance of early stage cancer would both improve the quality of life (QOL) of participants and save on the costs of screening programs. In this regard, there seems to be a growing consensus that annual PSA testing is not necessary for all participants[5–8] and the discrimination of men who can benefit from (or safely omit) annual PSA testing has been the central issue to design more cost-effective screening programs.

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* Corresponding author. Present address: Department of Urology, Kyoto University Graduate School of Medicine, Shogoinkawahara-cho 54, Sakyo-ku, Kyoto 606-8507, Japan. Tel.: +81 (0)75 751 3329; fax: +81 (0)75 751 3740.
E-mail address: selecao@kuhp.kyoto-u.ac.jp (T. Kobayashi).
[d] Research Fellow of The Japan Society for the Promotion of Sciences (DC1).

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Hugosson et al. conducted biennial PSA testing in all participants ($n = 20{,}000$), who were randomized to screening groups irrespective of baseline PSA levels. Their results suggested that a biennial strategy can detect more clinically significant cancers before they become symptomatic compared with a control group without mass screening.[5] According to a report by Ito et al., however, 45% of cancers detected at one year after a negative PSA result of 2.0 to 4.0 ng/ml were extracapsular disease or metastatic disease;[6] thus it seems risky to put a 2-year interval for men with baseline PSA levels of 2.0 to 4.0 ng/ml.

Some previous reports clearly show that baseline PSA levels have a very important role in the determination of optimal intervals to rescreen for prostate cancer[6–8] and that a personalized screening program would be developed with this concept. Until now, to the best of our knowledge, no clinical trials have been completed to evaluate the effect, safety and cost of prostate cancer rescreening strategies based on individual baseline PSA.

Here, we have created decision-analytic models of prostate cancer screening in which the biennial rescreening interval was applied based on individual baseline PSA levels and evaluated the cost-effectiveness of personalized prostate cancer screening strategies on the basis of quality-adjusted life years of participants.

Materials and methods

Design of decision-analytic models

Markov decision-analytic models of whether to screen for prostate cancer annually or biennially were created (Fig. 1) based on probability and outcome data from previously published literature using TreeAge Pro 2005 software (TreeAge Software, Inc., Williamstown, Massachusetts, USA). As shown in Fig. 2, participants were stratified by initial PSA level (baseline PSA) and the age-related probabilities of PSA increase to >4.0 ng/ml from each baseline PSA range group was determined according to Ito's report on a prostate cancer screening program undertaken since 1981 in Gunma Prefecture, Japan (Table 1).[9] Five screening strategies at annual or biennial PSA testing intervals according to baseline PSA levels were examined. Strategy A was designed as all participants have annual PSA testing irrespective of the baseline PSA levels, whereas participants with the baseline PSA levels of ≤1.0 (strategy B), ≤2.0 (C), ≤3.0 (D), ≤4.0

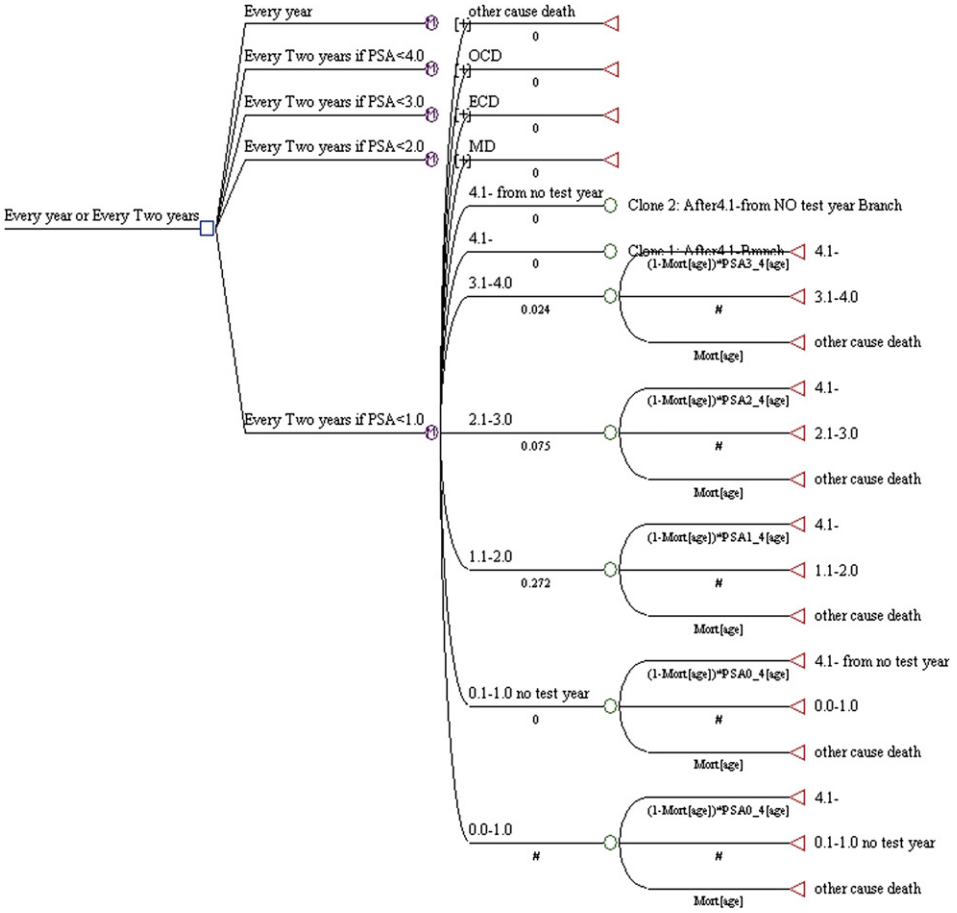

Figure 1. Markov tree for prostate cancer screening models representing strategy B (biennial screening in participants with baseline PSA ≤1.0 ng/ml). Details for the other strategies were left out.

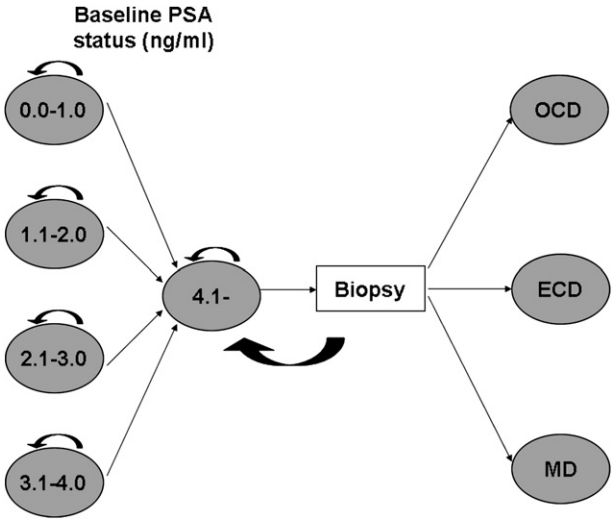

Figure 2. Schematic outline of the model structure.

(E) ng/ml are screened biennially in the other strategies, respectively. The screening algorithm comprised PSA measurement in every participant without routine digital rectal examination (DRE) or transrectal ultrasonography (TRUS), and participants with serum PSA levels >4.0 ng/ml were recommended to undergo TRUS-guided systematic biopsy.

Assumed parameters to run the models

At the initial setting, the proportions of men with PSA levels of 1.0 or less, 1.1 to 2.0, 2.1 to 3.0 and 3.1 to 4.0 ng/ml were determined as 62.9, 27.2, 7.5 and 2.4%, respectively.[9] Other variables with regard to clinical probabilities, costs and QOL were assumed based on the literature and actual medical cost (Table 2).[9–12] Based on the report by Djavan et al., cancer detection rate in the base case analysis was determined as 22%,[10] and participants with a positive PSA result but a negative biopsy result are to go back to the Markov status of PSA >4.0 ng/ml.

All detected cancers were categorized clinically into organ-confined disease (OCD, $cT_{1-2}N0M0$), extracapsular but non-metastatic disease (ECD, $cT_{3-4}N0M0$) and metastatic disease (MD, $TxN_1$and/orM_1). The distribution of the clinical stages was determined as 95.0% OCD, 3.0% ECD and 2.0% MD for men diagnosed to have cancer in a screening program (Table 2). In men who neglected to undergo biopsy despite a positive result of PSA testing or omitted PSA testing according to biennial screening strategy and consequently diagnosed to have cancer next year, disease stage varies due to the prolonged screening interval; the determinations were 90.0% (−5%) OCD, 7.0% (+4.0%) ECD and 3.0% (+1.0%) MD.[12] Rate of clinically insignificant cancer was assumed equivalent irrespective of screening interval.

Evaluation of outcomes

Outcomes for the decision-analytic model were expressed in total costs for diagnosis and treatment of prostate cancer and quality-adjusted life years (QALY) as effectiveness. QALY was calculated by multiplication of expected life years and QOL utilities assumed based on the literature (Table 2). To evaluate the impact of age on the outcome and the determination of an optimal strategy for the screening interval, we considered study cohorts of different ages at the initial setting of entry to the screening program; 50, 55, 60, 65 and 70 years; though we considered the cohort of 50-year-old men as the base case. In each case, cohorts are analyzed up to 80 years of age. Thus, the length of time of our analysis changes as the initial age of the cohort changes. Both costs and outcomes are discounted annually by a constant rate of 3%. Although our perspective is societal, costs such as of informal care and unrelated medical costs are not considered due to data availability.

Incremental cost-effectiveness ratio and sensitivity analysis

The incremental cost-effectiveness ratio (ICER; costs required to improve QALY unit) was calculated for comparisons between the strategies studied. Since several of the input parameters estimated from previous reports for this analysis might have been inconclusive, sensitivity analyses were run to test all assumptions of the model. Impact of

Table 1
Base case probabilities of PSA elevation to >4.0 ng/ml at a year after negative PSA results

Baseline PSA	Age range of participants (years)		
	50–59	60–69	70–
0.0–1.0 ng/ml	0.001 (0.0005, 0.002, 0.004)	0.002 (0.001, 0.003, 0.008)	0.002 (0.001, 0.003, 0.008)
1.1–2.0 ng/ml	0.002 (0.0001, 0.003, 0.008)	0.01 (0.005, 0.02, 0.03)	0.004 (0.002, 0.006, 0.012)
2.1–3.0 ng/ml	0.017 (0.01, 0.025, 0.03)	0.041 (0.02, 0.05, 0.06)	0.022 (0.01, 0.03, 0.04)
3.1–4.0 ng/ml	0.316 (0.25, 0.35, 0.40)	0.250 (0.20, 0.30, 0.35)	0.306 (0.25, 0.35, 0.40)

Based on a previous report by Ito et al.[9] Numbers in parenthesis represent low, intermediate and high values for sensitivity analysis, respectively.

Table 2
Assumption of clinical variables used in the base case and sensitivity analysis of the decision-analytic model

Variables	Value (range)	ICER changes in sensitivity analysis
Cancer detection rate on biopsy[10,15,16]	0.220 (0.20–0.40)	0.28–0.49
Proportion of stage on immediate biopsy[12]		
Organ-confined disease (OCD)	0.94	
Extracapsular disease (ECD)	0.03	
Metastatic disease (MD)	0.03	
Stage migration by differed biopsy[a,12]		
Organ-confined disease	−5.0% (−5–−20%)	1.03
Extracapsular disease	+4.0% (+2.5–+10%)	1.00
Metastatic disease	+1.0% (+1.0–+5.0%)	1.00
Biopsy rate in men with PSA >4.0 ng/ml[17]	0.60 (0.30–0.80)	1.03–1.04
Recurrence rate in OCD[18]	0.05 (0.05–0.20)	1.28
Recurrence rate in ECD[18,19]	0.75 (0.60–0.80)	0.99
Mean leading time to recurrence (years)[18,19]	5	
Mean prognosis in MD (years)[20,21]	3 (2–5)	1.34
Cost (US$)[22,23]		
PSA test	10.9 (5.0–20.0)	4.15–12.1
Biopsy	270.6	
Treatment of OCD	20,000 (10,000–30,000)	1.02–1.49
Treatment of ECD	51,818 (30,000–60,000)	0.98–1.00
Treatment of MD	45,455 (30,000–60,000)	0.56–0.98
Other cause of death	0	
Quality of life utility[22,24]		
Curable disease	0.9 (0.6–0.9)	0.58
Metastatic disease	0.5 (0.3–0.6)	1.17
Recurrent disease	0.7 (0.5–0.8)	1.00
Start age (years)	50 (50, 55, 60, 65, 70)	1.61–2.24
Age-related probabilities of PSA elevation[b]	low, intermediate, high	5.90–42.69

[a] Cancers assumed as diagnosed at 1 year after development due to neglect to undergo biopsy or omission according to a biennial screening strategy.
[b] Detailed probabilities are shown in Table 1.

changes in every assumption on ICER was expressed as the rate of the extreme ICERs in the range of assumed values (“ICER changes in sensitivity analysis” in Table 2); ICER changes in sensitivity analysis of 1.00 or equivalent mean less impact of the assumption on ICER and those far greater or less from 1.00 mean that the assumption has deep impact on ICER.

Results

Base case results

Strategy A with annual PSA testing irrespective of baseline PSA showed a cumulative cancer incidence of 1.76% at the first 5 years. When we considered a cohort consisting of men who were 50 years old at the initial setting of entry to the screening program, the cumulative cancer detection rate at 80 years old (30 years after entry) was simulated to be 10.4%. Cumulative detection of organ-confined cancer (OCD) in each strategy is similar among the strategies and ranges 92.6 to 93.1%.

Cost-effectiveness analysis

Strategy D (biennial screening in participants with baseline PSA $\leq$3.0 ng/ml) is the most cost-effective with respect to no screening policy. Strategy A (annual PSA testing in all participants), B (biennial PSA testing if baseline PSA is $\leq$1.0 ng/ml) and C (biennial PSA testing if baseline PSA is $\leq$2.0 ng/ml) are more effective but costs more and less cost-effective compared with strategy D. Strategy E (biennial PSA testing if baseline PSA is $\leq$4.0 ng/ml) is dominated by strategy D (more costly but less effective). In terms of the base cases, ICERs for strategies A, B and C with respect to strategy D, the most cost-effective strategy, are US$165,938, US$46,505 and US$5925, respectively.

Sensitivity analysis

As a result of sensitivity analysis for the clinical assumptions, the outcome that strategy D is the most cost-effective are robust against all assumed parameters used in this model. In terms of most clinical and economical parameters, ICERs showed monotone increases or decreases according to the changes in the assumed parameters. Among them, cost of PSA test seems to have the strongest effect on the ICER, followed by cancer detection rate on biopsy and annual discount rate (Table 2). Contrary, biopsy rate in participants with a positive PSA result, recurrence rates in OCD and ECD, prognosis in MD, treatment costs and quality of life utilities seem to have less impact on the outcomes of cost-effective analysis.

In terms of start age at which subjects participate to the screening program, however, ICERs for strategy A, B and C with respect to strategy D do not show monotone change. ICERs decrease with the start age being higher from the base case value of 50 years, then come to the lowest when the start age is 60, and thereafter become larger again according to the increase in the start age. ICER changes in the sensitivity analysis for start age ranged 1.61 to 2.24.

We also performed a sensitivity analysis in which the age-related probabilities of PSA increase to >4.0 ng/ml from each baseline PSA range group are changed. In this analysis, cost-effectiveness of each strategy is examined for low, intermediate and high probabilities compared to values for the base case analysis (Table 1). The analysis shows the robust results that strategy D is the most cost-effective against the variety of the probabilities of PSA increase. The lower probability of PSA increase is associated with the greater ICERs between strategy D and the other strategies. ICER changes in the sensitivity analysis

for the age-related probabilities of PSA increase ranged 5.90 (strategy C) to 42.69 (strategy A).

Discussion

Personalized rescreening strategy is cost-effective

One of the very important findings of this study is that biennial rescreening strategy for all men with a negative PSA result (≤4.0 ng/ml, strategy E) is not feasible since it is dominated (less effective but more costly) by other strategies. Clearly, it is because increased cost burden for advanced cancer due to inappropriately long intervals exceeds the cost savings by the reduction in the number of PSA test. The results of this study indicate that uniformly biennial screening is not only risky but also less cost-effective.

The findings seem discrepant with Hugosson's report indicating that there was no significant difference in the detection rate of clinically significant cancers between a biennial screening strategy and no screening strategy.[5] It seems to be partly because the results of the previous study indicating the effectiveness of a biennial screening strategy were based on a comparison between a biennial screening group and a control group not participating in a screening program. Another compelling explanation is that our model incorporates the probability of participants with rapid increases in serum PSA as reported by Ito et al.[6] As well, the main outcome of our model is not the cancer detection rate but cost-effectiveness regarding participants' QALY.

Another important implication derived from the present study is that uniformly annual screening strategy for every participant (strategy A) is too costly compared with other strategies. Cost and ICER of this strategy are prominent compared to the other strategies (Table 3). When the strategy D with biennial screening in men with PSA levels ≤3.0 ng/ml is considered, omission of annual PSA testing in men with baseline PSA levels of 3.0 ng/ml or less who accounts for 97.6% of participants, save the cost of PSA testing by 48.8%. As well as in the base case, the ICER for strategy A far exceeds an acceptable ICER range in most settings of sensitivity analyses for assumed variables. These robust results indicate that the uniform strategy with every year PSA testing seems to be too costly in any society under variable medical and economical conditions.

The most important consequence of this study is that personalized rescreening strategies using individual baseline PSA for the determination of the screening intervals are even cost-effective compared to conventional uniform rescreening strategies with annual or biennial PSA testing for every participant. There have been some previous reports indicating that every year screening can be safely omitted in men with low baseline PSA with regard to the detection of early cancer.[5–8] This study provides novel evidence that such personalized rescreening strategies have an advantage of cost-effectiveness.

Implication of incremental cost-effectiveness ratio and sensitivity analyses

Although strategy D with biennial screening in men with PSA levels ≤3.0 ng/ml is the most cost-effective of all strategies analyzed (Table 3), the authors do not intended that this cut-off value is absolute and universal. Compared with strategy D, strategies A, B and C cost more and are more effective in terms of improvement of participants QALY resulted from the increased detection of early cancer. Therefore, which strategy of A, B, C and D should be adopted depends on ICER threshold for willingness to pay, although the ICERs for strategy A are too high at any settings as described above. There has been no definitive consensus for ICER threshold. When we consider a threshold ICER of US$25,000/QALY for instance according to the report by Gazelle et al.,[13] strategy C would be more feasible than strategy D with the ICER of US$5925/QALY, whereas strategy A and B would not with the ICER of US$165,938 and 46,505/QALY, respectively.

Although the sensitivity analyses for most assumptions shows linear changes in ICERs for strategy A to C, ICER changes are not linear with regard to the sensitivity analysis for start age. Most ICERs for strategies A, B and C with respect to strategy D tend to decrease according to the age increase up to 60 and to increase thereafter. ICERs at age 60 are US$25,697 and 1941/QALY for strategy B vs

Table 3
End-cohort result

	Strategy	Cost (US$)	Effect (QALY)	ICER (US$/QALY)[a]	C/E[b]	OCD rate (%)[c]
A	All annual	1171.70	17.15121	165,938	68.32	93.10
B	Biennial if PSA ≤1.0	1113.50	17.15094	46,505	64.92	92.98
C	Biennial if PSA ≤2.0	1090.50	17.15056	5925	63.58	92.82
D	Biennial if PSA ≤3.0	1086.80	17.15016	–	63.37	92.66
E	Biennial if PSA ≤4.0	1087.50	17.14994	Dominated	63.41	92.56

[a] ICER: incremental cost-effectiveness ratio (costs required to improve QALY unit).
[b] Cost-effectiveness.
[c] Proportion to organ-confined disease to all prostate cancers detected throughout screening program.

D and C vs D, respectively, which are lower or equivalent compared to generally recommended thresholds for willingness to pay. Based on the findings, it may be recommended that cut-off baseline PSA for annual PSA testing can be lowered in 60's participants while cut-offs for 50's and 70's are kept as $\leq$3.0 ng/ml according to a society-specific threshold for willingness to pay. This seems to be one of interesting implications derived from the current study that is useful for the practical design of a screening program.

Sensitivity analyses showed strong impact of age-related probabilities of PSA increase to >4.0 ng/ml on ICER. Although it is thoroughly robust that personalized rescreening strategies are cost-effective, which strategy (cut-off) of them to be applied should be carefully considered for each society because probabilities of PSA increase can vary according to the distribution of age and race of the population. Cost of PSA testing also has a strong impact on ICER change in sensitivity analysis indicating that saving the cost of PSA testing is an important policy issue. The strong impact of PSA cost is not surprising in considering that the number of primary screening participants markedly varies according to each strategy. For example, the number of PSA testing in strategy B with biennial screening for men with PSA levels of 1.0 ng/ml or less is estimated about two-thirds of that in strategy A with annual screening for all men. In addition, a strong impact of cancer detection rate on ICER indicates that recent endeavors to modify prostate biopsy (e.g. increasing the number of core) with improved cancer detection rate will provide a considerable contribution to save ICERs for more effective strategies.

Limitations of the study

There are some limitations of this study. Since the study evaluated cost-effectiveness upon QALY, there has to be some evidence of effectiveness. There are some emerging evidence that population-based prostate cancer screening is beneficial and decrease disease-specific mortality,[3] the definitive conclusion is unclear until large randomized control trials ongoing eventually show a mortality benefit from PSA screening. Until then, therefore, the results of this study should be carefully interpreted as the application is limited to where PSA screening is effective.

There may be criticisms of the use of Markov model for a study on prostate cancer screening; analysis of a screening program seems too complex to create a universal model. There may be simpler decision analysis models expressing similar results as ours. In addition, the outcome of models may not be equally applied to individuals. There should be wide variation as an individual strategy may be beneficial for some but not for others.

The age-related PSA distribution and probabilities of PSA elevation were based largely on one study[9] since there have been a few published works with detailed data. To complement the lack of tangible data, a careful and comprehensive sensitivity analyses with respect to these assumptions were performed and robust results in terms of PSA cutoff for biennial screening were obtained. In terms of initial PSA distribution, another assumption that is 50% of participants have PSA <1 ng/ml[5] was tested and obtained similar results including cumulative cancer detection (8.5%) and cost-effectiveness. Nevertheless, our results would need to be validated with actual detailed data obtained by different investigators especially from other regions of the world. If application of our model to another screening program of elsewhere is considered, collection of proper data and modification of the model are possible for reanalysis for validation.

Although the outcomes of our model are quite similar to those of actual screening programs indicating that the model can express results of actual screening programs in the literature, lifetime risk to get a diagnosis of prostate cancer of 10.7% seems higher than generally expected. It seems because of the modeling in which participants with a negative biopsy result are to go to Markov status of PSA >4.0 ng/ml and to undergo biopsy every year. We created another model as the extreme opposite, in which participants with a negative biopsy result are never to get a diagnosis of prostate cancer through life. The modified model resulted in lifetime prostate cancer risk of 3.7% and similar outcomes in terms of cost-effectiveness and sensitivity analyses.

There may be a criticism that the model does not simulate the entire societal perspective due to the lack of data on informal care and unrelated medical costs. We did not define the direct impact of participating in a prostate cancer screening program on QOL. Despite a simple screening program that included only PSA testing, it is likely that participation in the screening program leads to impairment of QOL for some men (e.g., those with false-positive PSA test results). On the other hand, there may be also positive aspects of participating in a prostate cancer screening program with respect to QOL. Taylor et al. demonstrated that participants in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial reported high levels of health-related QOL and satisfaction with their decision to participate.[14] It is also reported that results of primary (PSA testing) and secondary (biopsy) screenings affect QOL and trial adherence of the participants. The assumption that rate of clinically insignificant cancer among OCD is equivalent irrespective of screening interval does not seem to influence significantly since the QOL utility for non-recurrent disease was determined high (0.95).

The current decision-analytic model was not designed that men with a negative biopsy result and men with the rapid PSA increase were categorized into specific groups with different risks of consequent diagnosis of prostate cancer. In addition, age-related values were not used for some assumptions including cutoff of PSA for biopsy, clinical relevance and treatment outcomes of diagnosed cancer due to data availability. If higher PSA cut-off and lower

clinical relevance had been applied to older population, strategy E (uniformly biennial screening with negative PSA participants) might not be dominated in this age range. However, these detailed stratifications of participants make the model very complex and require more number of hypothetical assumptions, which eventually would make the model rather impractical.

Since the ranges of variables for sensitivity analysis were not determined based on the standard deviation, direct comparison of the impact of each variable on ICER may not be appropriate. It was inevitable because available data for the deviation of these assumptions are quite limited. However, the ranges used for sensitivity analysis have been derived from the various reports to improve the reliability. Therefore, the authors believe that the sensitivity analysis in this study comprehends the actual range of the parameters. For more practical analysis, it is necessary to investigate actual values in individual socioeconomical system with which the model should be reanalyzed specifically.

In conclusion, our decision analysis demonstrated, in terms of cost-effectiveness, the adequacy to determine optimal screening intervals by baseline PSA incorporating clinical, social and economical conditions specific to a relevant population where prostate cancer mass screening is effective. Our results strongly support a personalized screening program based on individual tumor marker profile to improve not only QOL of the participants but also medical finance for health care.

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