Original Article

Comparative Effectiveness of Prostate Cancer Screening Between the Ages of 55 and 69 Years Followed by Active Surveillance

Tiago M. de Carvalho, PhD [1,2]; Eveline A. M. Heijnsdijk, PhD [1]; and Harry J. de Koning, PhD[1]

BACKGROUND: Because of the recent grade C draft recommendation by the US Preventive Services Task Force (USPSTF) for prostate cancer screening between the ages of 55 and 69 years, there is a need to determine whether this could be cost-effective in a US population setting. **METHODS:** This study used a microsimulation model of screening and active surveillance (AS), based on data from the European Randomized Study of Screening for Prostate Cancer and the Surveillance, Epidemiology, and End Results Program, for the natural history of prostate cancer and Johns Hopkins AS cohort data to inform the probabilities of referral to treatment during AS. A cohort of 10 million men, based on US life tables, was simulated. The lifetime costs and effects of screening between the ages of 55 and 69 years with different screening frequencies and AS protocols were projected, and their cost-effectiveness was determined. **RESULTS:** Quadrennial screening between the ages of 55 and 69 years (55, 59, 63, and 67 years) with AS for men with low-risk cancers (ie, those with a Gleason score of 6 or lower) and yearly biopsies or triennial biopsies resulted in an incremental cost per quality-adjusted life-year (QALY) of $51,918 or $69,380, respectively. Most policies in which screening was followed by immediate treatment were dominated. In most sensitivity analyses, this study found a policy with which the cost per QALY remained below $100,000. **CONCLUSIONS:** Prostate-specific antigen–based prostate cancer screening in the United States between the ages of 55 and 69 years, as recommended by the USPSTF, may be cost-effective at a $100,000 threshold but only with a quadrennial screening frequency and with AS offered to all low-risk men. ***Cancer*** **2018;124:507-13.** *© 2017 American Cancer Society.*

KEYWORDS: active surveillance, microsimulation model, overdiagnosis, prostate cancer.

INTRODUCTION

Frequent prostate-specific antigen (PSA)–based screening in the United States has led to concerns that a substantial proportion of screen-detected men may be overdiagnosed and overtreated. These concerns led the US Preventive Services Task Force (USPSTF) to recommend against prostate cancer screening in 2012.[1] In 2017, the USPSTF issued a draft statement recommending shared decision making between the ages of 55 and 69 years.[2] This in part due to the emergence of active surveillance (AS) as the main option for treating low-risk, screen-detected men in the United States.[3,4]

However, this recommendation leaves many open questions, including whether prostate cancer screening combined with immediate treatment or AS can be cost-effective, how frequently men should be screened between the ages of 55 and 69 years, and how AS should be performed after screen detection.

Most previous modeling efforts in prostate cancer screening[5-13] have not included either the quality of life or the costs or have not modeled AS. Heijnsdijk et al[5] simulated many screening policies for the Netherlands and suggested that only very limited screening (stopping at the age of 59 years) could be cost-effective, but explicit modeling of AS was not included. Previous studies that have modeled delayed treatment or AS suggest that AS is safe,[6,7] is less costly,[8-10] and may substantially reduce overtreatment.[6,7] One recent study compared the cost-effectiveness of delayed treatment and immediate treatment and found that screening with conservative management may be cost-effective.[11] However, that study did not fully model AS and did not consider the role of different AS protocols.

In this study, we present estimates of the cost-effectiveness of screening policies based on the USPSTF draft statement in combination with immediate treatment for all men or AS for low-risk (Gleason score of 6) and/or intermediate-risk men (Gleason score of 3 + 4 or lower).

Corresponding author: Tiago M. de Carvalho, Department of Public Health, Erasmus Medical Center, Dr. Molewaterplein 50, Rotterdam, the Netherlands 3015GE; t.decarvalho@erasmusmc.nl

[1]Department of Public Health, Erasmus Medical Center, Rotterdam, the Netherlands; [2]Department of Applied Health Research, University College London, London, United Kingdom.

See editorial on pages 453-5, this issue.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.31141, **Received:** May 30, 2017; **Revised:** July 18, 2017; **Accepted:** July 27, 2017, **Published online** December 12, 2017 in Wiley Online Library (wileyonlinelibrary.com)

MATERIALS AND METHODS

Simulation Model

MISCAN is a microsimulation model designed to evaluate the effects of prostate cancer screening. A detailed description is available at http://cisnet.cancer.gov/prostate/profiles.html and in previously published studies.[7,13-15]

The natural history model contained 18 health states corresponding to the combinations of 3 stages (T1, T2, and T3), 3 grades (Gleason score <7, Gleason score of 7, and Gleason score >7), and the cancer's metastasis status (yes or no). Additional states were created to model AS. Men at stage T2 with a Gleason score of 6 were classified as T2a or T2bc, and men with a Gleason score of 7 were classified as $3+4$ or $4+3$ according to their remaining lead time and age group. Initially, natural history parameters, which included the onset of the disease, durations, and transition probabilities between health states, were calibrated to observed European Randomized Study of Screening for Prostate Cancer (ERSPC) incidence data. This model was adapted to the US situation by the addition of an extra hazard of clinical diagnosis and by the acquisition of United States–specific estimates for other parameters from Surveillance, Epidemiology, and End Results (SEER) data.

The prostate cancer survival without treatment was assigned at clinical detection and depended on the Gleason score. It was estimated on the basis of SEER data from the pre-PSA era (1983-1986). To correct for improvements in survival not directly associated with screening or primary treatment, we added a hazard ratio of 0.82 for prostate cancer survival, which was calibrated to the observed prostate cancer mortality in the ERSPC control (no-screening) group.[7]

In case the patient was screen-detected and referred to AS, natural history progressed as if he had not been screen-detected. A patient might exit AS because of Gleason or volume progression (which it was assumed could occur only after an increase in stage) in each biopsy round, because of personal preference, or if he would be clinically detected at the time. The probabilities of referral to radical treatment were estimated on the basis of Johns Hopkins AS observed treatment-free survival data, with the rate of disease progression based on our natural history model.[16] For intermediate-risk men, we assumed that the probabilities of referral to treatment, given progression, were similar to those for low-risk men (Table 1 and Supporting Table 1 [see online supporting information]).

The hazard ratios for prostate cancer survival after radical treatment were 0.56 for radical prostatectomy according to Bill-Axelson et al[17] and 0.63 for radiation therapy (when we maintained the same ratio of benefit between radical prostatectomy and radiation therapy from Etzioni et al[18]). The effect of screening was dependent on the remaining lead time for nonmetastatic cases:

$$\text{Cure probability} = \exp(\text{Cure parameter} \times \text{Lead time})$$

The cure parameter was calibrated to the observed prostate cancer mortality reduction in the ERSPC trial after 11 years of follow-up and equaled -0.22.[7]

Screening and AS protocols

We simulated several cohorts by year of birth and on the basis of US life tables for a total of 10 million men. The age distribution of the sampled men was selected to match the observed age distribution in the United States during 1973-2005. According to the new USPSTF draft recommendation, men were screened between the ages of 55 and 69 years with different screening frequencies. Attendance was assumed to be 90%, the PSA threshold for biopsy referral was 4 ng/ml, and biopsy compliance was

TABLE 1. Modeling Referrals to Treatment in Active Surveillance

Event	Modeling	Parameter
Volume progression	Indirectly modeled; may occur if, in the absence of screening, there would be an increase in the T stage	Probability of volume progression given an increase in the T stage
Gleason upgrade	Directly modeled; may occur if, in the absence of screening, the Gleason score would increase	Sensitivity for a Gleason upgrade
Clinical diagnosis[a]	Time of clinical detection in the absence of screening	Hazard of clinical diagnosis per stage
Referral to treatment in the absence of progression	Randomly selected from all men in active surveillance	Probability of treatment in the absence of evidence of progression or clinical diagnosis

The parameters of the natural history model are calibrated to data from the European Randomized Study of Screening for Prostate Cancer and the Surveillance, Epidemiology, and End Results Program.[7,13,14] The parameters related to referral to treatment during active surveillance are calibrated to Johns Hopkins active-surveillance cohort data,[16] including the number of men experiencing volume progression or a Gleason upgrade, the number of men treated without evidence of progression, and the 5-year treatment-free survival (Supporting Table 1 [see online supporting information]). If referred to treatment, patients are equally distributed between radiation therapy and radical prostatectomy.

[a] For the clinical diagnosis event, all the related parameters are calibrated to Surveillance, Epidemiology, and End Results data and denote an additional hazard of clinical detection in the United States in comparison with the European situation.

equal to 41% on the basis of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO).[19]

After detection, we simulated several treatment pathways. We compared the immediate treatment situation with the assignment of low-risk men (stage T2a, Gleason score of 6, and PSA level < 10 ng/ml) to AS followed by yearly biopsies. Other AS protocols also included intermediate-risk men or a triennial interval between biopsies after the first year. We assumed that all men classified as low-risk were selected for AS. The biopsy compliance during AS was based on Prostate Cancer Research International: Active Surveillance–observed biopsy compliance[20] (Supporting Table 2 [see online supporting information]).

Quality of Life and Costs

Quality-adjusted life-years (QALYs) were calculated with utility estimates ranging from 0 (death or worst imaginable health) to 1 (full health). Utility estimates and durations concerning all stages of early detection and treatment were similar to those of Heijnsdijk et al.[21] We assumed 1 week of utility loss (0.99) due to screening attendance and 3 weeks due to biopsy (0.90). We divided posttreatment utility loss into 3 phases (<2 months, 2-12 months, and 1-9 years). In particular, the utility for the postrecovery period from radical treatment (1-9 years) was calculated on the basis of Stewart et al[22] and Sanda et al[23] (Supporting Table 3 [see online supporting information]). During AS, utility loss could occur because of repeat biopsies. The costs of screening were based on Hayes et al.[24] The cost of immediate treatment was an estimate from another simulation model[25] and included posttreatment surveillance costs. Costs of palliative therapy were based on Yabroff et al.[26] Costs did not include indirect costs (except in a sensitivity analysis; Table 2).

Outcomes

We estimated the cost-effectiveness of each AS protocol and immediate treatment. The main outcome was the incremental cost-effectiveness ratio. The average cost per QALY gained was relative to the situation with no screening, and it was assumed that every clinically detected man was treated immediately. We also showed cancers diagnosed and overdiagnosed, prostate cancer mortality and life-years, and the overall cost of the screening program.

Sensitivity Analyses

To assess the effect of uncertainty around the parameter estimates on the outcomes, several multivariate sensitivity analyses were performed; they included the utility and cost estimates for each event, the parameters of the model related to the treatment benefit and referral to treatment during AS, the benefit due to early detection, and the effect of discounting (Table 3).

TABLE 2. Utilities, Durations, and Costs of Screening and Treatment

Event	Utility	Duration, y	Cost, US $
Screening	0.99	0.02	151
Biopsy	0.90	0.06	743
Cancer diagnosis	0.80	0.08	—
RT, < 2 mo	0.73	0.16	23,565[a]
RT, 2-12 mo	0.78	0.84	
RP, < 2 mo	0.67	0.16	16,946[a]
RP, 2-12 mo	0.77	0.84	
AS (surveillance costs)[b]	—	6	245/y
Postrecovery	0.95[c]	9	
Palliative therapy	0.60	2.5	48,472[d]
Terminal illness	0.40	0.5	

Abbreviations: AS, active surveillance; RP, radical prostatectomy; RT, radiation therapy.
All utilities and durations are based on Heijnsdijk et al.[21] The costs of screening are based on Hayes et al.[24]
[a] The costs of RP and RT include surveillance costs.[25]
[b] The surveillance costs of AS include 4 prostate-specific antigen tests and 1 visit to the physician per year for 6 years. These costs do not yet include the cost of biopsy because this depends on the AS protocol.
[c] Based on data from Stewart et al[22] and Sanda et al.[23] For the calculation, see Supporting Table 3 (see online supporting information).
[d] Based on Yabroff et al.[26]

RESULTS

Effects

In Table 4, the effects of yearly screening followed by immediate radical treatment or AS are shown. One hundred fifty-eight cancers per 1000 screened men were diagnosed, and 53 were screen-detected; this resulted in 23 overdiagnosed cancers and in prostate cancer mortality reductions of 23% and 21% for immediate treatment and AS, respectively. We estimated, at a 3% discount rate, that 30 life-years were saved by screening, but with an adjustment for the quality of life, this number was reduced to 17 (see Supporting Table 4 for the undiscounted values [see online supporting information]).

With all low-risk patients referred to AS, the life-years gained were reduced to 28; however, QALYs increased to 18. Selecting intermediate-risk men for AS resulted in 16 QALYs gained.

Reducing the frequency of screening to every 2 years resulted in approximately 14 to 15 QALYs gained, depending on the AS protocol; 10 to 11 QALYs were gained with quadrennial screening.

Costs

The costs of screening yearly and treatment between the ages of 55 and 69 years, with respect to the no-screening

TABLE 3. Overview of Included Uncertainty in the Multivariate Sensitivity Analyses

Parameters	Value	Range
Cure parameter	−0.22	−20% to + 20%
Hazard ratios for treatment and baseline survival		
Hazard ratio of improvement in baseline survival	0.82	−20% to + 20%
Hazard ratio of RP	0.56	0.41-0.77[a]
Hazard ratio of RT	0.63	0.46-0.87[a]
Active-surveillance parameters		
Sensitivity to Gleason progression	0.4	−20% to + 20%
Probability of detection of volume upgrade (T2a)	0.1	−20% to + 20%
Probability of detection of volume upgrade (>T2a)	0.5	−20% to + 20%
Probability of referral to treatment without progression	0.04	−20% to + 20%
Utilities (favorable/unfavorable)[b]		
Screening	0.99	1.00-0.98
Biopsy	0.90	0.87-0.94
Cancer diagnosis	0.80	0.85-0.75
RT, < 2 mo	0.73	0.75-0.71
RT, 2-12 mo	0.78	0.88-0.68
RP, < 2 mo	0.67	0.78-0.56
RP, 2-12 mo	0.77	0.84-0.70
Postrecovery	0.95[c]	0.93-0.97
Palliative therapy	0.60	0.24-0.86
Terminal illness	0.40	0.24-0.56

Abbreviations: RP, radical prostatectomy; RT, radiation therapy.
In 2 additional separate analyses, all costs were varied by 50% more and less, and the cost-effectiveness was recalculated with 0% and 6% discounts.
[a] The confidence interval for the hazard ratio is shown. The confidence interval for RP was taken from Bill-Axelson et al.[17] The confidence interval for RT was extrapolated with the same ratio used by Etzioni et al.[18]
[b] Adapted from Heijnsdijk et al.[5] *Favorable/unfavorable* refers to whether the utility gives more/fewer quality-adjusted life-years gained by screening, respectively.
[c] Based on Heijnsdijk et al,[5] Stewart et al,[22] and Sanda et al.[23] For details, see Supporting Table 3 (see online supporting information).

situation, were approximately $1.8 million for immediate treatment for 1000 screened men and $1.7 million for AS with yearly biopsies. When we reduced the frequency to every 2 or 4 years, the costs become $1.0 million or $0.6 million per 1000 screened men, respectively.

Average Cost per QALY

The costs per QALY gained of screening men yearly between the ages of 55 and 69 years and treating every man immediately were approximately $103,037. When low-risk men were referred to AS with yearly or 3-year biopsies, this cost was reduced to $91,979 or $91,654, respectively. Screening every 2 or 4 years resulted in a cost per QALY of $73,590 or $55,673, respectively.

Incremental Cost-Effectiveness

Of all the screening and AS policies considered, we determined which were the most efficient according to their incremental cost-effectiveness. Most policies in which screening was followed by immediate treatment or in which screening was followed by AS for low- and intermediate-risk men were dominated; that is, they were more expensive and resulted in fewer QALYs gained.

Screening between the ages of 55 and 69 years every 4 years (at the ages of 55, 59, 63, and 67 years) and offering AS to low-risk men with yearly or triennial biopsies resulted in an incremental cost per QALY lower than the $100,000 threshold.

Multivariate Sensitivity Analyses

In the multivariate sensitivity analyses, we focused on screening between the ages of 55 and 69 years every 4 years. When the set of unfavorable utilities was used, the (incremental) cost per QALY significantly increased in all cases, and AS with yearly biopsies, which was efficient in the base case, became dominated. With the set of favorable utilities, immediate treatment dominated the other alternatives (Supporting Table 5 [see online supporting information] and Fig. 1). Computing the cost-effectiveness with a 6% discount rate resulted in a situation in which no policy had a cost per QALY lower than $100,000. If there was no discounting, AS would lose its advantage, and immediate treatment would become cost-effective (Supporting Table 5 and Fig. 1).

We also varied several sets of model parameters. In all situations, immediate radical treatment and AS for low- and intermediate-risk men remained dominated. In particular, a lower hazard ratio for treatment and baseline survival (more lives saved by treatment) resulted in a higher cost per QALY in all cases. Varying the probabilities of referral from AS to immediate treatment had a low impact on the cost per QALY of AS (Supporting Table 6 [see online supporting information] and Fig. 1).

DISCUSSION

In this study, we estimated the costs and effects associated with screening followed by AS or immediate treatment in comparison with no screening in the US population. We found that between the ages of 55 and 69 years, only quadrennial screening (55, 59, 63, and 67 years) with AS for low-risk men could be cost-effective at a $100,000 threshold. Strategies in which immediate treatment is offered to all men are dominated by strategies in which AS is offered to low-risk men; that is, AS results in more QALYs gained and lower costs than immediate treatment.

Our findings are consistent with those of Heijnsdijk et al,[5] who found that only very limited screening can be cost-effective, and Roth et al,[11] who found that screening

TABLE 4. Costs and Effects of IRT Versus AS per Screening Intensity

Screening Policy	Treatment[a]	Screen-Detected, No.	Overdiagnosis, No.	PCM Reduction, %	LYs	QALYs	Total Cost[b]	Average Cost per QALY, US $	ICER, US $[c]
55-69 y, every 4 y[d]	AS, 3 y			11	14.6	10.3	0.54	51,918	51,918
	AS, intermediate			10	13.6	9.6	0.55	57,052	Dominated
	AS, yearly			11	15.4	10.6	0.56	52,398	69,380
	IRT	27	11	12	16.0	10.2	0.57	55,673	Dominated
55-69 y, every 2 y	AS, 3 y			16	21.3	14.6	0.96	65,631	100,613
	AS, intermediate			16	19.8	13.6	0.98	72,549	Dominated
	AS, yearly			18	22.7	15.0	1.00	66,643	106,032
	IRT	44	18	18	23.8	14.0	1.03	73,590	Dominated
55-69 y, yearly	AS, 3 y			19	25.8	17.8	1.63	91,654	Weakly dominated
	AS, intermediate			19	24.2	16.2	1.68	103,484	Dominated
	AS, yearly			21	28.0	18.4	1.69	91,979	201,719
	IRT	53	23	23	29.8	16.9	1.75	103,037	Dominated

Abbreviations: AS, active surveillance; ICER, incremental cost-effectiveness ratio; IRT, immediate radical treatment; LY, life-year; PCM, prostate cancer mortality; QALY, quality-adjusted life-year.

Effects per 1000 screened men are shown. Costs and effects are discounted at 3%. QALYs were calculated by the multiplication of the loss in utility with the duration of the phase and the number of men who experienced the event, as predicted by MISCAN (see Supporting Table 4 for additional effects [see online supporting information]).

[a] IRT could be either radical prostatectomy or radiation therapy (equal probability). *Yearly* indicates yearly biopsies, *3 y* indicates biopsy every 3 years after the first year, and *intermediate* indicates the admission of low- and intermediate-risk patients for AS with yearly biopsies.

[b] The total cost includes costs for screening, treatment, and palliative therapy, which we assume was given to all men who died of prostate cancer. Net costs were calculated from the difference between the total costs in a situation without screening and the total costs in a situation with screening. Costs are shown in millions of 2015 US dollars.

[c] A policy is classified as dominated if there is another policy that has a lower cost and results in more QALYs gained. Weakly dominated policies are less effective policies that have a higher cost-effectiveness ratio than the next ranked policy.

[d] Screening was performed at the ages of 55, 59, 63, and 67 years.

with conservative management is more cost-effective than screening with immediate treatment. In addition, previous studies of AS have shown that it has the potential to significantly reduce the harms of prostate cancer screening while keeping a large portion of the benefit.[6-11]

Our sensitivity analyses show that these findings are robust to changes in the most important model parameters, utilities and costs, although the most efficient screening and AS protocol may change. The only scenarios in which AS would lose its advantage in comparison with immediate treatment would occur if we did not use discounting or if we used the set of more favorable utilities toward screening and treatment. Screening every 4 years with AS may result in an incremental cost per QALY higher than $100,000 if we were to increase the discount rate to 6%.

Our study links the cost-effectiveness of screening between the ages of 55 and 69 years with different AS protocols. Furthermore, our model has a natural history of prostate cancer in which all transition probabilities between the different disease stages were calibrated to the observed incidence in a large randomized control trial (ERSPC).[27] We adapted this to the US context by adding US life tables and US screening patterns and by adapting the rate of clinical diagnosis and sensitivity to match the observed incidence of prostate cancer in the United States with SEER data. The probabilities of referral to treatment during AS were estimated on the basis of the observed treatment-free survival in the Johns Hopkins cohort.[16] In contrast to Roth et al,[11] we modeled AS explicitly.

The results of this study are also subject to some limitations. The costs of treatment were obtained from the lifetime estimates from another microsimulation model,[25] and they do not include the costs of salvage treatment. We found that the utility estimates have a significant effect on the cost per QALY. In particular, the results are sensitive to the utility of treatment postrecovery because it has a duration of 9 years by assumption.

We considered screening only within the age group of 55 to 69 years; however, previous studies have suggested that lowering the stopping age may significantly reduce overdiagnosis,[5,12,13] and a recent study has found that PSA screening between the ages of 50 and 55 years could also be beneficial.[28] Therefore, screening in this age group is likely not optimal.

Our AS model uses a simplification of the actual criteria for selection and later referral to treatment. For instance, although our model uses the PSA, T stage, and Gleason score as selection criteria, most AS cohorts also use the number of positive biopsy cores or PSA density.[29] The probabilities of referral to treatment during AS are

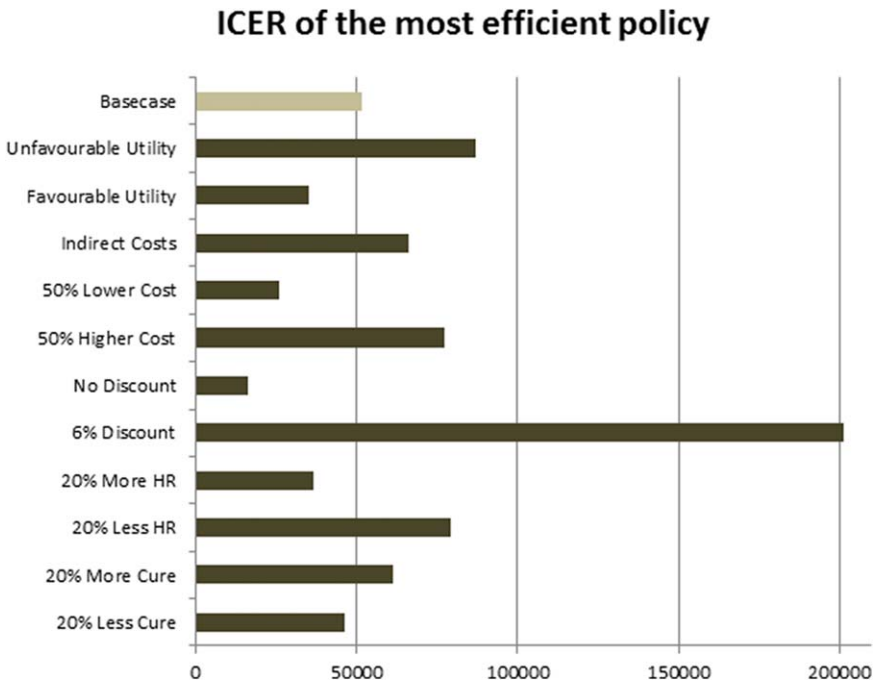

Figure 1. Incremental cost-effectiveness ratio (ICER) under different modeling assumptions. The base case includes the cost per quality-adjusted life-year of screening every 4 years between the ages of 55 and 69 years with a prostate-specific antigen threshold for biopsy referral of 4 ng/ml and a biopsy compliance rate of 41% (in the screening phase) in comparison with no screening and immediate treatment. The active-surveillance protocol in the base case consists of yearly biopsies, with biopsy compliance taken from observed Prostate Cancer Research International: Active Surveillance data.[20] *20% more HR* denotes a 20% higher HR for the benefit of immediate treatment; that is, fewer lives are saved by treatment. HR indicates hazard ratio; ICER, incremental cost-effectiveness ratio.

based on a single cohort,[16] and our model of AS assumes 100% referral of low-risk men to AS, whereas in the United States, this is likely far from 100%.[3] These results may not be applicable to the African American population because of the higher incidence of the disease[30] or to men with significant comorbidities, who will likely not benefit from PSA screening.[31]

Because PSA is not very specific for the detection of high-risk prostate cancer, many efforts are underway with the goal of decreasing overdiagnosis and/or improving the detection of high-risk cancers with genetic markers,[32] biomarkers,[33,34] risk calculators,[35] panels of many markers,[36] and magnetic resonance imaging (MRI)–guided biopsy.[37] For instance, genetic tests could be applied before the PSA test to divide men into different risk categories, and risk-stratified screening policies could be applied; men at higher risk would be screened more intensively.[32] After an elevated PSA test, risk calculators[35,36] or MRI[37] could be used to decide whether men should go through prostate biopsy and/or to improve the selection of men for AS. These developments will likely significantly improve the efficacy of screening in terms of QALYs gained because many men will avoid biopsy and a cancer diagnosis. However, costs in the diagnosis phase could also substantially increase according to MRI usage.

Prostate cancer screening is still a controversial topic. The 2 major randomized controlled trials of prostate cancer screening, ERSPC[27] and PLCO,[38] showed conflicting results for the effect of prostate cancer screening on prostate cancer mortality, likely because of the large amount of screening in the control group of the PLCO trial.[39] With modeling, we can weigh the number of life-years gained, with the burden experienced by the many men who are unnecessarily diagnosed and treated, and we can evaluate whether PSA screening is worthwhile. In this study, we have found that screening between the ages of 55 and 69 years combined with AS for low-risk men could be cost-effective at a $100,000 threshold if the screening frequency remains low (quadrennial) and AS is offered to all low-risk men (Gleason score of 6 and stage T2a or lower).

FUNDING SUPPORT

This work was supported by the National Cancer Institute (grants U01 CA157224 and U01 CA199338) as part of the Cancer Intervention and Surveillance Modeling Network. Its contents are solely

the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

CONFLICT OF INTEREST DISCLOSURES

The Department of Public Health of the Erasmus Medical Center received a research grant from Beckman-Coulter, Inc, to study the cost-effectiveness of Prostate Health Index testing.

AUTHOR CONTRIBUTIONS

Tiago M. de Carvalho: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, and visualization. **Eveline A. M. Heijnsdijk**: Conceptualization, methodology, writing–review and editing, and supervision. **Harry J. de Koning**: Supervision, project administration, and funding acquisition.

REFERENCES

1. Moyer VA; US Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2012;157:120-134.
2. Bibbins-Domingo K, Grossman DC, Curry SJ. The US Preventive Services Task Force 2017 draft recommendation statement on screening for prostate. *JAMA Oncol.* 2017;317:1949-1950.
3. Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990-2013. *JAMA.* 2015;314:80-82.
4. Bangma CH, Valdagni R, Carroll PR, van Poppel H, Klotz L, Hugosson J. Active surveillance for low-risk prostate cancer: developments to date. *Eur Urol.* 2015;67:646-648.
5. Heijnsdijk EA, de Carvalho TM, Auvinen A, et al. Cost-effectiveness of prostate cancer screening: a simulation study based on ERSPC data. *J Natl Cancer Inst.* 2015;107:366.
6. Xia J, Trock BJ, Cooperberg MR, et al. Prostate cancer mortality following active surveillance versus immediate radical prostatectomy. *Clin Cancer Res.* 2012;18:5471-5478.
7. de Carvalho TM, Heijnsdijk EAM, de Koning HJ. Estimating the risks and benefits of active surveillance protocols for prostate cancer: a microsimulation study. *BJU Int.* 2017;119:560-566.
8. Corcoran AT, Peele PB, Benoit RM. Cost comparison between watchful waiting with active surveillance and active treatment of clinically localized prostate cancer. *Urology.* 2010;76:703-707.
9. Eldefrawy A, Katkoori D, Abramowitz M, Soloway MS, Manoharan M. Active surveillance vs. treatment for low-risk prostate cancer: a cost comparison. *Urol Oncol.* 2013;31:576-580.
10. Keegan KA, Dall'Era MA, Durbin-Johnson B, Evans CP. Active surveillance for prostate cancer compared with immediate treatment: an economic analysis. *Cancer.* 2012;118:3512-3518.
11. Roth JA, Gulati R, Gore JL, Cooperberg MR, Etzioni R. Economic analysis of prostate-specific antigen screening and selective treatment strategies. *JAMA Oncol.* 2016;2:890-898.
12. Gulati R, Gore JL, Etzioni R. Comparative effectiveness of alternative prostate-specific antigen–based prostate cancer screening strategies. *Ann Intern Med.* 2013;158:145-153.
13. de Carvalho TM, Heijnsdijk EA, de Koning HJ. Screening for prostate cancer in the US? Reduce the harms and keep the benefit. *Int J Cancer.* 2015;136:1600-1607.
14. Draisma G, Postma R, Schroder FH, van der Kwast TH, de Koning HJ. Gleason score, age and screening: modelling dedifferentiation in prostate cancer. *Int J Cancer.* 2006;119:2366-2371.
15. Draisma G, Boer R, Otto SJ, et al. Lead time and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst.* 2003;95:868-878.
16. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol.* 2011;29:2185-2190.
17. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med.* 2014; 370:932-942.
18. Etzioni R, Gulati R, Tsodikov A, et al. The prostate cancer conundrum revisited: treatment changes and prostate cancer mortality declines. *Cancer.* 2012;118:5955-5963.
19. Pinsky PF, Andriole GL, Kramer BS, et al; Prostate, Lung, Colorectal and Ovarian Project Team. Prostate biopsy following a positive screen in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. *J Urol.* 2005;173:746-750.
20. Bokhorst LP, Alberts AR, Rannikko A, et al; PRIAS Study Group. Compliance rates with the Prostate Cancer Research International Active Surveillance (PRIAS) protocol and disease reclassification in noncompliers. *Eur Urol.* 2015;68:814-821.
21. Heijnsdijk EA, Wever EM, Auvinen A, et al. Quality-of-life effects of prostate-specific antigen screening. *N Engl J Med.* 2012;367:595-605.
22. Stewart ST, Lenert L, Bhatnagar V, Kaplan RM. Utilities for prostate cancer health states in men aged 60 and older. *Med Care.* 2005;43:347-355.
23. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med.* 2008;358:1250-1261.
24. Hayes JH, Ollendorf DA, Pearson SD, et al. Observation versus initial treatment for men with localized, low-risk prostate cancer: a cost-effectiveness analysis. *Ann Intern Med.* 2013;158:853-860.
25. Laviana AA, Ilg AM, Veruttipong D, et al. Utilizing time-driven activity-based costing to understand the short- and long-term costs of treating localized, low-risk prostate cancer. *Cancer.* 2016;122:447-455.
26. Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. *J Natl Cancer Inst.* 2008;100:630-641.
27. Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med.* 2012;366:981-990.
28. Carlsson S, Assel M, Ulmert D, et al. Screening for prostate cancer starting at age 50-54 years. A population-based cohort study. *Eur Urol.* 2017;7:46-52.
29. Simpkin AJ, Tilling K, Martin RM, et al. Systematic review and meta-analysis of factors determining change to radical treatment in active surveillance for localized prostate cancer. *Eur Urol.* 2015;67:993-1005.
30. Tsodikov A, Gulati R, de Carvalho TM, et al. Is prostate cancer different in black men? Answers from 3 natural history models. *Cancer.* 2017;123:2312-2319.
31. Lansdorp-Vogelaar I, Gulati R, Mariotto AB, et al. Personalizing age of cancer screening cessation based on comorbid conditions: model estimates of harms and benefits. *Ann Intern Med.* 2014;161:104-112.
32. Eeles RA, Olama AA, Benlloch S, et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet.* 2013;45:385-391.
33. Lazzeri M, Haese A, de la Taille A, et al. Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2-10 ng/ml: a multicentric European study. *Eur Urol.* 2013;63:986-994.
34. Wei JT, Feng Z, Partin AW, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer? *J Clin Oncol.* 2014;32: 4066-4072.
35. Poyet C, Nieboer D, Bhindi B, et al. Prostate cancer risk prediction using the novel versions of the European Randomised Study for Screening of Prostate Cancer (ERSPC) and Prostate Cancer Prevention Trial (PCPT) risk calculators: independent validation and comparison in a contemporary European cohort. *BJU Int.* 2016;117:401-408.
36. Gronberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. *Lancet Oncol.* 2015;16:1667-1676.
37. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA.* 2015;313:390-397.
38. Andriole GL, Crawford ED, Grubb RL, et al. Mortality results after 13 years of follow-up. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med.* 2009;360:1310-1319.
39. Pinsky PF, Blacka A, Kramer BS, Miller A, Prorok PC, Berg C. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. *Clin Trials.* 2010;7:303-311.