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Quality-of-Life Effects of Prostate-Specific Antigen Screening

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ABSTRACT

BACKGROUND

After 11 years of follow-up, the European Randomized Study of Screening for Prostate Cancer (ERSPC) reported a 29% reduction in prostate-cancer mortality among men who underwent screening for prostate-specific antigen (PSA) levels. However, the extent to which harms to quality of life resulting from overdiagnosis and treatment counterbalance this benefit is uncertain.

METHODS

On the basis of ERSPC follow-up data, we used Microsimulation Screening Analysis (MISCAN) to predict the number of prostate cancers, treatments, deaths, and quality-adjusted life-years (QALYs) gained after the introduction of PSA screening. Various screening strategies, efficacies, and quality-of-life assumptions were modeled.

RESULTS

Per 1000 men of all ages who were followed for their entire life span, we predicted that annual screening of men between the ages of 55 and 69 years would result in nine fewer deaths from prostate cancer (28% reduction), 14 fewer men receiving palliative therapy (35% reduction), and a total of 73 life-years gained (average, 8.4 years per prostate-cancer death avoided). The number of QALYs that were gained was 56 (range, –21 to 97), a reduction of 23% from unadjusted life-years gained. To prevent one prostate-cancer death, 98 men would need to be screened and 5 cancers would need to be detected. Screening of all men between the ages of 55 and 74 would result in more life-years gained (82) but the same number of QALYs (56).

CONCLUSIONS

The benefit of PSA screening was diminished by loss of QALYs owing to postdiagnosis long-term effects. Longer follow-up data from both the ERSPC and quality-of-life analyses are essential before universal recommendations regarding screening can be made. (Funded by the Netherlands Organization for Health Research and Development and others.)

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After a median follow-up of 9 years, the initial results of the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a significant relative reduction of 20% in prostate-cancer mortality among men undergoing prostate-specific antigen (PSA) screening, with a reduction of 27% after adjustment for selection bias.[1] In recently updated results at 11 years, the relative reduction in prostate-cancer mortality in the screening group was 29% after adjustment for selection bias.[2] At the Gothenburg center in the ERSPC, there was a reduction of 44% in prostate-cancer mortality after a median follow-up of 14 years among all men (including those who had not actually undergone screening) and a 56% reduction for men who had undergone screening at least once.[3] In the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, investigators found no mortality reduction in the screening group; however, the rate of contamination with respect to nonstudy screening in the control group was high, and the rate of biopsy compliance was low.[4]

Obvious benefits of screening for prostate cancer are a reduction in disease-related mortality, an increase in the number of life-years gained, and a reduction in the rate of advanced disease. However, PSA screening is associated with substantial unfavorable effects. In the ERSPC screening group, the cumulative incidence of prostate cancer was 7.4%, as compared with 5.1% in the control group.[2] A proportion of the screen-detected tumors (10 to 56%) would never have led to clinical symptoms,[5-8] but these overdiagnosed cancers are frequently treated, with associated risks of adverse effects.[9] Furthermore, because of a long lead time until clinical symptoms would develop from screen-detected tumors (estimated at 5 to 12 years[6,10]), men would have an increased number of years of living with these adverse effects.

Reports on the harms and benefits of PSA screening have been highly inconsistent owing to the lack of results from randomized screening trials.[11,12] However, as more mature data from the ERSPC are available, realistic predictions of the effects of screening can be made. Therefore, in this study, we have quantified the effects of screening strategies both on prostate-cancer mortality and on quality of life using a model that is based on data from the ERSPC. In addition, we have determined the harms and benefits for a range of treatment, mortality-reduction, and screening scenarios.

Methods

ERSPC Data

The ERSPC was initiated in the early 1990s to evaluate the effect of PSA screening on prostate-cancer mortality.[13] In seven countries, 162,243 men underwent randomization to undergo PSA testing or not to undergo PSA testing. Most centers used a PSA cutoff value of 3.0 ng per milliliter as an indication for biopsy, whereas others used a cutoff of 4.0 ng per milliliter, with additional tests for values between 2.5 and 4.0 ng per milliliter. The screening interval was 4 years, with the exception of Sweden, where it was 2 years. Treatment was performed according to local policies and guidelines, independent of the study group.[14] In line with the protocol, the effect of screening in the core age group (55 to 69 years) was evaluated. Follow-up data on mortality through December 31, 2008, are currently available.[2]

In this study, we used a Microsimulation Screening Analysis (MISCAN) model to extrapolate the ERSPC data to alternative screening strategies and an extended follow-up.

Screening Strategies

We simulated a male population between the ages of 0 and 100 years with an age distribution that was based on the European Standard Population.[15] The following screening strategies were simulated: annual screening in men between the ages of 55 and 69 years and in those between the ages of 55 and 74 years, screening at 4-year intervals among men between the ages of 55 and 69 years, and single screening performed at the age of 55 years, 60 years, or 65 years. A rate of participation of 80% in screening was assumed.

Quality of Life

We predicted the number of quality-adjusted life-years (QALYs) associated with screening using utility estimates for various health states. The utility estimates were obtained from the Cost-Effectiveness Analysis Registry[16] and additional studies (Table 1)[17-33] and ranged from 0 (death or worst imaginable health) to 1 (full health). In addition, we analyzed data from ERSPC on treatment-related complications, such as urinary incontinence, bowel dysfunction, and erectile dysfunction. Favorable and unfavorable values were assigned according to the minimum and maximum values in the cited references. A utility estimate of 0.99 was used for the screening phase, because prostate-cancer

Table 1. Utility Estimates and Durations for Various Health States.

Health State	Utility Estimate			Source of Utility Estimate	Duration	Source of Duration†
	Base	Favorable	Unfavorable			
Screening attendance	0.99	1.00	0.99	Essink-Bot et al.[17] and de Haes et al.[18]	1 wk	Assumption
Biopsy	0.90	0.94	0.87	de Haes et al.[18]	3 wk	Assumption
Cancer diagnosis	0.80	0.85	0.75	Korfage et al.[19]	1 mo	Assumption
Radiation therapy						
At 2 mo after procedure	0.73	0.91	0.71	Stewart et al.[20]	2 mo	Stewart et al.[20]
At >2 mo to 1 yr after procedure	0.78	0.88	0.61	Konski et al.[21]	10 mo	Sanda et al.[22]
Radical prostatectomy						
At 2 mo after procedure	0.67	0.90	0.56	Stewart et al.[20]	2 mo	Stewart et al.[20]
At >2 mo to 1 yr after procedure	0.77	0.91	0.70	Calvert et al.[23]	10 mo	Sanda et al.[22]
Active surveillance	0.97	1.00	0.85	Bennett et al.,[24] Zeliadt et al.,[25] and Cooperberg et al.[26]	7 yr	van den Bergh et al.[27]
Postrecovery period	0.95	1.00	0.93	Sanda et al.[22] and Stewart et al.[20]	9 yr*	Assumption
Palliative therapy	0.60	0.24	0.86	Konski et al.,[29] Moeremans et al.,[30] Penson et al.,[31] and Ramsey et al.[32]	30 mo	Damber and Aus[33]
Terminal illness	0.40	0.24	0.40	Konski et al.,[29] Penson et al.,[31] and Ramsey et al.[32]	6 mo	Penson et al.[31] and Ramsey et al.[32]

* The duration of the postrecovery period that was used for the sensitivity analysis was the residual lifetime.[28]
† Assumption refers to the authors' conclusion after discussion with experts.

screening has little effect on short-term health status and anxiety.[17] The health states of men receiving treatment were divided into 2 months of treatment, an intermediate period (10 months of recovery after treatment), and a postrecovery period (1 to 10 years after treatment). We obtained utility estimates for this postrecovery period by combining the percentage of men with side effects from the treatment[22] with the utility estimates for those side effects.[20] This led to a utility estimate of 0.95 for all men during the period of 1 to 10 years after diagnosis and after receiving radical prostatectomy or radiation therapy. We calculated the loss in quality of life by multiplying the loss in utility by the duration of the health state and the number of men in that state as predicted by MISCAN.

MISCAN MODEL

We used MISCAN to model prostate-cancer screening.[5,6] This model simulates individual life histories stochastically (i.e., involving chance or probability). The natural history of prostate cancer starts with a transition from cancer-free to preclinical screen-detectable prostate cancer in a subgroup of the population. From each preclinical stage, the tumor may be screen-detected, be diagnosed clinically, or progress into a more advanced preclinical stage.

In the model, prostate cancers were characterized according to their clinical T stage (T1, impalpable; T2, palpable and confined to the prostate; and T3+, palpable with extension beyond the prostatic capsule), differentiation grade (Gleason score ≤7, 7, or ≥7), and metastatic stage (locoregional or distant). We first estimated the measurements for the natural history of the disease and for stage-specific test sensitivities (0.82 to 0.98, depending on clinical T stage and Gleason score) using incidence in the Dutch population during the period from 1992 through 2002 (a period with limited opportunistic screening)[34] and using age and stage distributions from the Rotterdam and Gothenburg centers (the largest sites in the ERSPC), which varied according to the method of randomization and recruitment, as well as screening intervals. In a second phase, we validated this model using screening data from all centers. The model and calibration methods and results are detailed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

In MISCAN, treatment assignment for men with locoregional prostate cancer was based on

the primary treatment (radiation therapy, radical prostatectomy, or active surveillance) that was assigned in the two study groups in ERSPC, according to age, disease stage, and Gleason score. All men with metastases and all men dying of prostate cancer were assumed to have received palliative treatment. The proportion of men receiving treatment within 7 years after the initiation of active surveillance was based on recent data.[35]

We modeled survival of unscreened men in whom locoregional prostate cancer was diagnosed using survival curves calculated on the basis of the Gleason score.[36] These data were obtained from a large unscreened cohort of men who were followed for a median of 24 years, and the data were available according to age, disease stage, and tumor grade. For distant disease, survival curves were based on Surveillance, Epidemiology, and End Results (SEER) data. We modeled the effects of treatment by assuming a relative risk of dying from prostate cancer of 0.65 for men undergoing radical prostatectomy,[37] as compared with watchful waiting. This effect was also assumed for radiation therapy.

A proportion of men with screen-detected locoregional prostate cancer will be cured. In the base model, we estimated the proportion of this stage-dependent cure by calibrating the model to a relative reduction of 29% in prostate-cancer mortality after 11 years of follow-up on the basis of screening at 4-year intervals for men who attended at least one screening, which corresponded to the ERSPC data.[2] This estimated cure proportion was used as an input to the model. We also estimated cure proportions for a hypothetical reduction of 31% in prostate-cancer mortality (the estimated reduction with adjustment for noncompliance and contamination),[38] for a reduction of 39% (the target reduction for the trial in the Gothenburg center) after 9 years of follow-up, and for a reduction of 56% after 14 years of follow-up (in the Gothenburg center).[3] In the model, among men who were found to have prostate cancer during screening, all those who were cured were estimated to have died from other causes at the time they would have died if the prostate cancer had not been diagnosed; those who were not cured were estimated to have died at the time they would have died if they had not been screened. The effects of screening were calculated from 2010 until 2110, by which time all the men would have died.

STUDY OVERSIGHT

This study was designed by the first and last author. ERSPC data were gathered at each study center and analyzed by the epidemiology committee. The first draft of the manuscript was written by the first author, with all coauthors participating in several revisions and in the decision to submit the manuscript for publication. There were no agreements concerning confidentiality of the data between the sponsors and the authors or their institutions.

RESULTS

QUALITY OF LIFE AFTER TREATMENT

Two specific studies on quality of life after prostate-cancer treatment have been performed for men participating in Rotterdam and Sweden.[9,39] Preoperatively, 1 to 2% of the men were incontinent and 31 to 40% were impotent. At 18 to 52 months after treatment, incontinence was reported in 6 to 16% of the men undergoing radical prostatectomy and in 3% of those undergoing radiation therapy (Table 2). At 6 to 52 months after treatment, impotence among men who were potent preoperatively was reported in 83 to 88% of those undergoing radical prostatectomy and in 42 to 66% of those undergoing radiation therapy. In general, men whose prostate cancer was detected during screening had fewer symptoms both preoperatively and postoperatively than did those whose cancer was clinically detected (Table S4 in the Supplementary Appendix). This difference could be a result of aging because of later diagnosis in the unscreened group. These ERSPC data are consistent with data from a large international cohort (Fig. S7 in the Supplementary Appendix).

BASE MODEL OF ANNUAL SCREENING

We modeled the effect of the various health states in both the presence and absence of annual screening over the lifetime of 1000 men between the ages of 55 and 69 years (Table 3). We also calculated the number of life-years and QALYs gained or lost as a result of the differences between the numbers of men within each health state. The model predicted that a total of 73 life-years would be gained through the introduction of annual screening in this group. The number of prostate-cancer diagnoses was predicted to increase from 112 cases to 157 cases (a relative increase of 40%). The number of prostate-cancer deaths was pre-

Table 2. Rates of Incontinence and Erectile Dysfunction Associated with Prostate-Cancer Treatments at Two ERSPC Centers.*

Side Effect and Treatment	Study Site	Rate of Side Effect				
		Preoperative	6 Mo	12 Mo	18 Mo	52 Mo
		percent				
Incontinence						
Regular daytime use of pads						
Radical prostatectomy (N=294)	Gothenburg	1	NA	NA	16	NA
Daily urinary leakage and use of ≥3 pads per day						
Radical prostatectomy (N=127)	Rotterdam	2	16	7	NA	6
Radiation therapy (N=187)	Rotterdam	1	1	1	NA	3
Erectile dysfunction†						
No sexual activity or impotent						
Radical prostatectomy (N=294)	Gothenburg	32	NA	NA	83	NA
Sexually active and erectile dysfunction or sexually inactive because of erectile dysfunction						
Radical prostatectomy (N=127)	Rotterdam	31	88	88	NA	88
Radiation therapy (N=187)	Rotterdam	40	42	43	NA	66

* NA denotes not available.
† The postoperative scores for erectile dysfunction are for men who had normal preoperative erectile function.

dicted to decrease from 31 to 22 (a relative decrease of 28% after rounding), and the number of men receiving palliative care was predicted to decrease from 40 to 26 (a relative reduction of 35%). The total number of life-years gained per prostate-cancer death avoided was 8.4 years. Among screened men, there was a reduction of 37% in prostate-cancer mortality over the entire lifetime (Table 4).

The predicted adverse effects of screening were 247 additional negative biopsies and 41 additional men receiving radical prostatectomy or radiation therapy. The model predicted a gain of 56 QALYs (range, –21 to 97), which means that 23% of the unadjusted life-years that were gained would be counterbalanced by a loss in quality of life. This loss was primarily attributable to the short-term and long-term effects of primary treatment and a longer postrecovery period with side effects.

We also calculated the number of QALYs that were predicted to be gained in the base model in sensitivity analyses that considered various assumptions for overdiagnosis, screening attendance, and utility estimates (Fig. 1). A hypothetical situation without overdiagnosis was predicted to yield a gain of 79 QALYs. Rates of screening attendance ranging from 50 to 100% were predicted to produce a gain of 30 to 60 QALYs (with 23% adjustment of 39 and 78 life-years gained, respectively). The most favorable utility estimates resulted in 97 QALYs gained, and the least favorable in 21 QALYs lost. The utility estimate for the post-recovery period had a considerable effect. If no loss in utility in this period was assumed, screening resulted in 72 QALYs gained, whereas a utility estimate of 0.93 instead of 0.95 for the remaining lifetime resulted in 6 QALYs gained. A utility estimate of 0.95 during the first 5, 7, or 15 years after diagnosis in combination with no loss in utility after that period resulted in a gain of 66, 62, and 47 QALYs, respectively (results not shown in graph). Other utility estimates besides those for the postrecovery period and for palliative therapy had a minor effect on the results.

In the base model, 104 cancers were detected during screening; of these cancers, 45 (43%) were overdiagnosed (Table 4). (Overdiagnosis was defined as the detection of a prostate cancer during screening that would not have been clinically diagnosed during the man's lifetime in the absence of screening.) The reduction in prostate-cancer mortality in a steady state (in which the

Table 3. Effect of Various Health States with and without Annual Screening for Prostate Cancer over the Lifetime of 1000 Men between the Ages of 55 and 69 Years.*

Health State	Utility Loss	No Screening	Screening	Difference between Screening and No Screening		Quality Adjustment
		no. of men			*no. of life-yr*†	*no. of life-yr (range)*‡
Screening attendance	–0.01	0	8242	8242	158	–1.6 (–1.9 to –0.3)
Biopsy	–0.10	313	605	292	17	–1.7 (–2.2 to –1.0)
Cancer diagnosis	–0.20	112	157	45	4	–0.7 (–0.9 to –0.6)
Radiation therapy						
At 2 mo after procedure	–0.27	43	48	5	1	–0.2 (–0.2 to –0.1)
At >2 mo to 1 yr after procedure	–0.22	43	48	5	4	–0.9 (–1.6 to –0.5)
Radical prostatectomy						
At 2 mo after procedure	–0.33	32	68	35	6	–2.0 (–2.7 to –0.6)
At >2 mo to 1 yr after procedure	–0.23	32	68	35	30	–6.9 (–9.1 to –2.7)
Active surveillance	–0.03	28	48	20	106	–3.2 (–15.8 to 0)
Postrecovery period						
No overdiagnosis	–0.05	75	71	–4	109	–5.5 (–36.4 to 0)
Overdiagnosis	–0.05	0	45	45	215	–10.8 (–30.3 to 0)
Palliative therapy	–0.40	40	26	–14	–35	14.1 (5.1 to 26.9)
Terminal illness	–0.60	31	22	–9	–4	2.6 (2.6 to 3.3)

* The rate of attendance at screenings was assumed to be 80%. The total adjustment in the number of life-years owing to all health effects was –16.7 (range, –93.8 to 24.4).
† The difference in the number of men who underwent screening and those who did not undergo screening has been multiplied by the duration of the health states (as shown in Table 1).
‡ The difference in life-years for each health state has been multiplied by the utility loss to calculate the adjustment for quality of life.

number of prevented deaths has stabilized 20 years after the start of screening) for men who attended at least one screening was estimated at 37%. We estimated that in order to prevent one prostate-cancer death, 98 men would need to be screened and 5 cancers would need to be detected.

The predicted effects of various cure rates on the basis of various mortality reductions are described in Table S5 in the Supplementary Appendix.

PREDICTED EFFECTS OF SCREENING STRATEGIES

The extension of the screening to the age of 74 years resulted in an overall gain of 82 life-years and an increase in the number of prostate-cancer deaths prevented from 9 to 11 (Table 4). However, the model predicts that only 56 QALYs (range, –47 to 111) would be gained, representing a 32% reduction in unadjusted life-years. This reduction in quality of life is mainly due to the large number of overdiagnosed cases (48% of cancers detected on screening) and the 372 additional negative biopsies that would occur. On the other hand, the number who would need to be screened (84) was more favorable than the number associated with screening up to the age of 69 years.

Screening at 4-year intervals among men between the ages of 55 and 69 years led to a gain of 52 life-years and 41 QALYs (range, –10 to 69). There was a reduction of 21% in the number of life-years gained after adjustment for quality of life, and the number who would need to be screened rose to 129.

Single screening at the age of 55 years, 60 years, or 65 years resulted in the detection of fewer cancers but also in less overdiagnosis, with a reduction of 27 to 31% in steady-state prostate-cancer mortality and a gain in life-years of 12 to 25. The number of men who would need to undergo single screenings at 55, 60, or 65 years of age in order to prevent one prostate-cancer death was 490, 249, and 186, respectively.

Table 4. Predicted Effects of Prostate-Cancer Screening, as Compared with No Screening, at Various Ages over the Lifetime of 1000 Men.*

Variable	Age at Screening					
	55–69 Yr (Base Model)	55–74 Yr	55–69 Yr	55 Yr Only	60 Yr Only	65 Yr Only
Screening data						
Interval (yr)	1	1	4	NA	NA	NA
Screening tests (no.)	8242	10,577	2250	548	584	588
Men invited for screening (no.)	853	891	833	685	730	735
Men who underwent screening (no.)	845	883	777	548	584	588
Effects						
Cancers diagnosed (no.)	45	73	29	3	9	19
Cancers detected on screening (no.)	104	150	70	8	23	42
Overdiagnosed cancers (no.)	45	72	29	2	8	19
Rate of overdiagnosis in cancers detected on screening (%)	43	48	41	30	35	45
Negative biopsies (no.)	247	372	166	18	52	102
Prostate-cancer deaths (no.)	–9	–11	–6	–1	–2	–3
Relative reduction in prostate-cancer mortality (%)†	37	41	32	27	29	31
Lead-time (yr)	1134	1508	750	106	262	419
Life-yr gained (no.)	73	82	52	12	22	25
QALYs gained (no.)	56	56	41	12	19	17
Relative reduction in life-yr gained after adjustment for quality of life (%)	23	32	21	6	15	33
Men who would need to be screened to prevent one prostate-cancer death (no.)	98	84	129	490	249	186
Cancers that would need to be detected to prevent one prostate-cancer death (no.)	5	7	5	2	4	6

* A reduction of 29% in prostate-cancer mortality after 11 years of screening at 4-year intervals was assumed. The rate of attendance at screenings was assumed to be 80%. In the unscreened scenario, there would be 112 cancers diagnosed, 201 negative biopsies, and 31 prostate-cancer deaths. NA denotes not applicable, and QALY quality-adjusted life-year.

† The relative reduction in prostate-cancer mortality reflects steady-state values after 20 years of screening for men who attended at least one screening.

DISCUSSION

Weighing the balance between the benefits and harms of prostate-cancer screening is essential for decision making regarding screening at both the individual and the policy level. Our model predicts that there would be nine fewer prostate-cancer deaths and 73 life-years gained over the lifetime of 1000 men who underwent annual screening between the ages of 55 and 69 years. The harms caused by the introduction of such screening would be the overdiagnosis and overtreatment of 45 cases and the loss of 1134 life-years free of prostate cancer (i.e., lead-time years). After adjustment of the number of life-years gained from screening by consideration of quality-of-life effects, 56 QALYs would be gained, which is a 23% reduction from the predicted number of life-years gained.

We used a 1-year screening interval in the base runs to comply with existing practice in the United States; however, the conclusions are similar with a 4-year interval.

In order to prevent one death from prostate cancer, the number of men who would need to be screened (98) and the number of cancers that would need to be detected (5) that were predicted in the base model are more favorable than the numbers reported in earlier ERSPC results

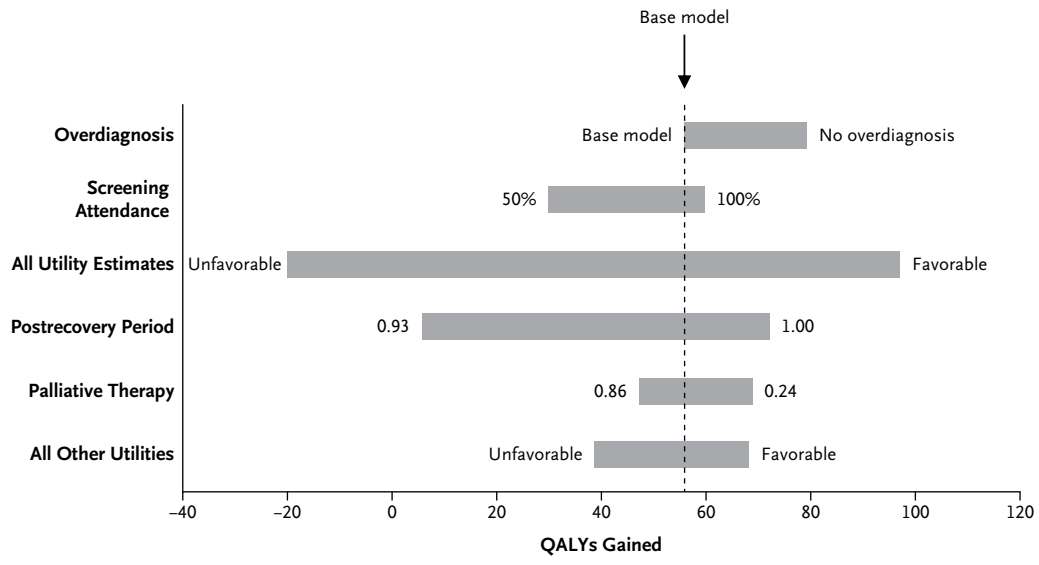

Figure 1. Effect of Various Modeling Assumptions on Quality-Adjusted Life-Years (QALYs) Gained by Prostate-Cancer Screening in Comparison with the Base Model.

The base model predicted a gain of 56 QALYs (range, –21 to 97) for men between the ages of 55 and 69 years who underwent prostate-cancer screening, which means that 23% of the unadjusted life-years gained by screening would be counterbalanced by a loss in quality of life because of follow-up biopsies and procedures. In the base model, sensitivity analyses considered various assumptions, including the effects of overdiagnosis, screening attendance of 50% and 100%, all unfavorable and favorable utility estimates, utility estimates of 0.93 and 1.00 for the lifetime postrecovery period, utility estimates of 0.86 and 0.24 for palliative therapy, and utility estimates for the postrecovery period (0.95) and palliative therapy (0.60) as used in the base model combined with the unfavorable and favorable utility estimates of all other health states.

(which predicted 1068 and 48, respectively).[1] The Gothenburg trial reported that 293 men would need to be screened and 12 cancers would need to be detected at 14 years of follow-up.[3] Our model predicts long-term effects after a much longer period. After 11 years, the cumulative incidence of prostate cancer in the ERSPC screening group far exceeded that in the control group (9.7 vs. 6.0 per 1000 person-years). However, the control group will partly catch up because of the lead time, and therefore the absolute difference between the groups will decrease. In addition, the absolute difference in the number of prostate-cancer deaths is likely to increase over time, reducing the numbers of men who would need to be screened and the number of cancers that would need to be detected.

A substantial part of the predicted difference between life-years and QALYs gained is caused by overdiagnosed cancers. The proportion of overdiagnosed cases (42% of cancers detected during screening) that was predicted in the base model is similar to that in previous studies.[6] Strategies to reduce overdiagnosis would seem to be necessary before screening can be generally advocated. Distinguishing indolent cancers from aggressive cancers will be crucial.[40,41] More active surveillance and deferring treatment until early signs of disease progression may also increase the QALYs gained.[42,43]

The optimal screening strategy can also depend on comorbidity status. In our model, we used general life tables for the rate of death from other causes, and therefore the distribution of comorbidity was that of a general population. We can roughly estimate the effect of comorbidity by adjusting the life tables. For example, for men who are 65 years of age who have the same life expectancy as men 62 years of age (low comorbidity), annual screening for prostate cancer between the ages of 55 and 69 resulted in 93 life-years gained and 80 QALYs gained (an adjustment of 14%), and

annual screening until the age of 75 years resulted in 108 life-years gained and 86 QALYs gained (an adjustment of 20%). Therefore, screening until the age of 75 years in men with low comorbidity has approximately the same adjustment for quality of life as screening until the age of 69 years in the general population.

The 23% predicted reduction in life-years gained due to quality-of-life effects is higher than the 8% estimated for breast-cancer screening.[18] In addition to cancer deaths avoided, screening for breast cancer allows the use of less radical treatment (e.g., lumpectomy vs. mastectomy) in early detected cancers, whereas screening for prostate cancer leads to a substantial increase in treatments, especially when active surveillance for indolent disease is not undertaken. Also, among women undergoing breast-cancer screening, an average of 15 life-years are gained per breast-cancer death that is prevented, whereas among men undergoing prostate-cancer screening, only 8.4 life-years are gained per prostate-cancer death that is prevented because of an older age at diagnosis and shorter life expectancy among men.

The predicted adjustment for quality of life is due to the long-term side effects from treatment. Men in whom cancer has been overdiagnosed and those in whom cancer has not been overdiagnosed will live many years with the adverse effects of treatment. For example, in the postrecovery period, 5 life-years were adjusted for men without overdiagnosis and 11 life-years for those with overdiagnosis. How these side effects influence the long-term quality of life has not been well studied. Most side effects affecting the urinary tract and bowel will improve after some years, but substantial symptoms persist in many patients up to 5 years after treatment.[22,44,45] Although patients can adapt to these effects,[46,47] partly because they consider themselves cured of a life-threatening disease (despite potential overdiagnosis), they still report lower physical functioning 5 to 10 years after treatment than a control group of similar age.[44,48,49] The results from a study of urinary, bowel, and sexual function over time after radical prostatectomy and radiation therapy, as measured as part of the ERSPC, have been compared with one of the largest studies outside the ERSPC[50] (Fig. S7 in the Supplementary Appendix). General patterns are similar, in that there is an improvement in function over time until a level slightly lower than baseline is reached (Fig. S7 in the Supplementary Appendix). A published analysis used a decremented post-treatment utility for lifetime.[33] In our base model, we used a utility estimate of 1 for the time period of more than 10 years after diagnosis, assuming improvement of symptoms.

One limitation of our model is that some of the utility estimates that we used were based on studies performed in the United States, and these results may not be representative of European populations. Also, we did not make corrections in utility estimates for the mode of cancer detection (screening or clinically detected),[47] for the individual baseline quality-of-life level,[51] or for improvements in treatments, owing to a lack of detailed data. It is obvious that an important goal is decreasing long-term morbidity from treatment. However, the perceived effect of treatment on quality of life is subjective. Therefore, general recommendations regarding screening do not necessarily apply to individual patients.

Another limitation of our model is that we used different data sets to develop the model. We used data from the ERSPC to estimate the measurements that are directly related to screening or that can be estimated only from such data (i.e., for the natural history of the disease). For other measurements, other sources were more appropriate, because of more extensive populations, more recent data, or longer follow-up. We mostly used data from Rotterdam and Gothenburg, because these two large centers have different screening intervals and recruitment and therefore this variation is reflected in the model. Also, the stage distributions match well those of the entire ERSPC and cover the entire age range. We found no important differences when we compared the sensitivity of PSA tests in Finland, Sweden, and the Netherlands.[52]

We assumed that radiation treatment would have survival effects similar to those of radical prostatectomy. No clinical trials have directly compared radical prostatectomy with radiation therapy, although some studies have shown a mortality benefit for radical prostatectomy over radiation therapy.[53,54] Assuming a relative risk of dying of 0.7 for radiation treatment would lead to an increase of a few percentage points in the number of QALYs.

In the Netherlands, men have a lifetime risk of death from prostate cancer of 3.5%. If screening reduced this probability by 30%, it would mean one fewer death per 100 men. This difference is too small to become significant in the rate of

death from any cause in our study but would have an important effect with respect to nationwide screening.

The next step should be calculating the cost-effectiveness of screening. However, to find the optimal screening strategy, studies should simulate more screening scenarios than the ones presented in this study, including various intervals, starting and stopping ages, and intervals that vary according to age.

In conclusion, this study quantifies how much of the benefit of the overall reduction in prostate-cancer mortality in the ERSPC must be adjusted when the harms are taken into consideration. It is essential to await longer follow-up data from the ERSPC, as well as longer-term data on how treatment and active surveillance affect long-term quality of life, before more general recommendations can be made regarding mass PSA screening.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article is dedicated to the memory of Stefano Ciatto, who provided thought-provoking insights into the benefits and harms of cancer screening.

APPENDIX

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