How Does Early Detection by Screening Affect Disease Progression? Modeling Estimated Benefits in Prostate Cancer Screening

Elisabeth M. Wever, MSc, Gerrit Draisma, PhD, Eveline A. M. Heijnsdijk, PhD, and Harry J. de Koning, MD, PhD

Background. *Simulation models are essential tools for estimating benefits of cancer screening programs. Such models include a screening-effect model that represents how early detection by screening followed by treatment affects disease-specific survival. Two commonly used screening-effect models are the stage-shift model, where mortality benefits are explained by the shift to more favorable stages, and the cure model, where early detection enhances the chances of cure from disease.* **Objective.** *This article describes commonly used screening-effect models and analyses their predicted mortality benefit in a model for prostate cancer screening.* **Method.** *The MISCAN simulation model was used to predict the reduction of prostate cancer mortality in the European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam. The screening-effect models were included in the model. For each model the predictions of prostate cancer mortality reduction were calculated. The study compared 4 screening-effect models, which are versions of the stage-shift model or the cure model.* **Results.** *The stage-shift models predicted, after a follow-up of 9 years, reductions in prostate cancer mortality varying from 38% to 63% for ERSPC-Rotterdam compared with a 27% reduction observed in the ERSPC. The cure models predicted reductions in prostate cancer mortality varying from 21% to 27%.* **Conclusions.** *The differences in predicted mortality reductions show the importance of validating models to observed trial mortality data. The stage-shift models considerably overestimated the mortality reduction. Therefore, the stage-shift models should be used with care, especially when modeling the effect of screening for cancers with long lead times, such as prostate cancer.* **Key words:** *cancer, screening, early detection, mortality reduction.* **(Med Decis Making 2011;31:550–558)**

Screening can be used for the early detection of several types of cancer.[1] For example, mammography is commonly used to detect breast cancer in an earlier stage and Pap smear is used to detect potentially precancerous lesions and prevent cervical cancer.[2] Screening for colorectal cancer with fecal occult blood test, flexible sigmoidoscopy, and colonoscopy has been tested in randomized trials.[3] Prostate-specific antigen (PSA) screening for the early detection of prostate cancer is widespread in the United States.[4] Death from cancer might be postponed or prevented if a cancer is found earlier because treatment is received at a less advanced stage. However, this benefit can only be obtained if the treatment that is received is more effective at a less advanced stage.

Models are often used to simulate the progression of cancer and how this progression is affected by screening. Such models are described as natural history models. They have been important tools for estimating benefits and harms of interventions for early detection, for instance, the screening of breast cancer,[5,6] cervical cancer,[7,8] and colorectal cancer.[9,10] Models have also been used to explain observed trends in cancer incidence and mortality. For example, Etzioni and others[11] used 2 models to project that 45% to 70% of the observed decline in prostate cancer mortality by year 2000 could plausibly be attributed to the stage-shift attributable to screening.

Address correspondence to Elisabeth M. Wever, MSc, Department of Public Health, Erasmus Medical Center, P.O. Box 2040, Rotterdam, The Netherlands; telephone: +31-10-7043884; fax: +31-10-7038474; e-mail: e.m.wever@erasmusmc.nl.
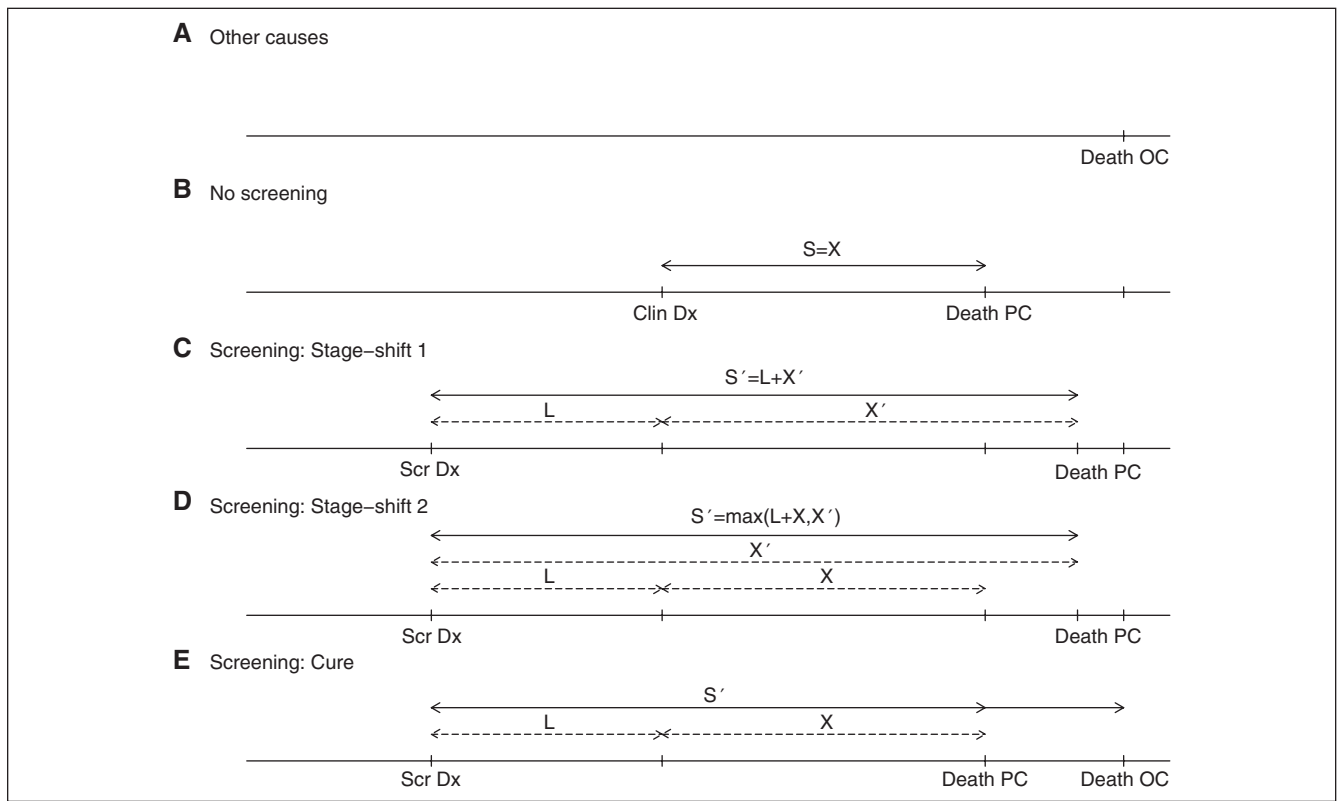
Figure 1   Modeling the impact of early detection on disease progression. Each panel shows relevant events in an individual life history on a time line. Panel A indicates the time of death from other causes than prostate cancer (Death OC). Panel B presents the prostate cancer history in the absence screening. Survival S after clinical diagnosis (Clin Dx) equals a random variable X, drawn from a survival curve specific for stage at diagnosis. Panels C through E illustrate the impact of early detection by screening in the various models. (C) With the stage-shift 1 model, survival S′ after detection by screening (Scr Dx) equals the sum of lead time L and a random variable X′ drawn from a survival curve specific for the stage at the time of early detection. (D) With the stage-shift 2 model, X′ is generated similarly, but survival after detection by screening S′ is taken to be the maximum of the original survival (L + X) and the new X.′ (E) In the cure models, survival S′ is up to death from other cause (Death OC) with probability c (cure) and equals the original survival corrected for lead time (L + X) with probability 1 – c (no cure).

Berry and others[12] showed with 7 models that mammography screening and treatment have helped to reduce the rate of death from breast cancer in the United States.

Natural history models include a screening-effect model. A screening-effect model determines how early detection by screening followed by treatment affects the progression of cancer, specifically how diagnosing and treating patients at a less advanced stage affects prostate cancer mortality. Screening-effect models can be summarized generally into 2 types. Stage-shift models attribute the better prognosis because of early detection by screening to the shift to a less advanced stage with the corresponding, more favorable stage-specific survival. Cure models assume that early detection is followed by curative treatment that is either successful in preventing cancer-specific

mortality or unsuccessful, that is, not changing the time and cause of death of patients. Mortality predictions from the models may vary significantly with the type of screening-effect model used. In this article we study the effect of various stage-shift and cure models on the predicted prostate cancer mortality in the European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam and compare this effect with the results observed in the overall ERSPC.[13]

METHODS

In most simulation models the progression of cancer in individuals is simulated first in the absence of screening (Figure 1B). In the absence of screening, the time of prostate cancer death is defined by survival, *S*, after clinical diagnosis which equals a random

EXPLORING MODEL STRUCTURE   **551**

Table 1 Parameters and Data Source for Each Screening-Effect Model

| Model | Parameters | Parameter Value by Stage at Diagnosis | | | Source |
		Local–Regional and Gleason Score ≤7	Local–Regional and Gleason Score >7	Distant and Any Gleason Score	
Stage-shift 1, 2A, 2B	Stage-specific survival at 5 years 10 years	0.98 0.90	0.73 0.49	No effect (0.45)[a] No effect (0.29)[a]	SEER prostate cancer–specific survival in pre-PSA era (1983–1986) with hazard ratio 0.65 from Bill-Axelson and others.[16]
Cure 1A	Stage-specific probability of cure	0.33	0.17	No effect	Ratio of long-term, prostate cancer–specific survival of nontreated and treated prostate cancer in pre-PSA era (SEER 1983–1986) with hazard ratio 0.65 from Bill-Axelson and others.[16] $[S(20)^{0.65} - S(20)] / [1 - S(20)^{0.65}]$
Cure 1B	Stage-specific probability of cure	0.42	0.23	No effect	Calibration to the observed 27% mortality reduction in ERSPC at 9 years of follow-up.[13]
Cure 2A	Stage-specific probability of cure	0–0.69: increasing with lead time up to 5 years	0–0.37: increasing with lead time up to 5 years	No effect	Calibration to the observed 27% observed mortality reduction in ERSPC at 9 years of follow-up.[13]

a. Value in parentheses is the prostate cancer–specific survival probability for patients detected with prostate cancer by clinical diagnosis. If prostate cancer is detected by screening in the distant stage, it is assumed that screening has no effect on the survival.

variable, *X*, drawn from a survival curve specific for stage at diagnosis.

These natural history models assume a preclinical phase that precedes the time of clinical diagnosis during which tumors can be detected by screening. How early detection by screening affects the modeled disease progression depends on the screening-effect model. The screening-effect model is a submodel that takes into account that persons diagnosed with cancer early by screening may have a better cancer-specific survival compared with persons clinically diagnosed when symptoms appear. In general, persons with cancers found by screening have better survival in part because there is a lead time component in the survival and also because finding and treating cancers earlier might postpone the time of death of cancer. This study considers 4 different screening-effect models: 2 stage-shift models and 2 cure models. Figure 1, C–E, illustrates the different models, and Table 1 presents the model parameters for the specific models.

Stage-Shift Models

Stage-shift models attribute the improved prognosis associated with early detection by screening to the shift to a less advanced cancer stage with the corresponding, more favorable stage-specific survival. A simple application of this principle is that a survival time from the moment of screen detection is generated from a stage (at detection) specific survival function, which is the same survival function as for men clinically diagnosed with cancer. This simple application may lead to implausible consequences: namely, that patients' lives may be shorter in the case of early detection by screening than in the case of no screening. This may be plausible, for example, if treatment is associated with mortality. However, because the mortality due to treatment is usually relatively small, this situation does not arise in most models. Most stage-shift models use an additional assumption to avoid implausible results of reduced life-expectancy with

screening. In this study we consider the following stage-shift models.

In stage-shift model 1, no death from cancer is allowed during lead time, that is, before the time of clinical diagnosis in the absence of screening. Technically, we assume that persons whose cancers are detected by screening have a cancer-specific survival, X', which depends on the stage, age, and treatment at screen detection and that the survival time starts after the lead time, L; that is, the survival starts at the expected time of clinical diagnosis in the absence of screening. This implies that the survival, S', after detection by screening equals the sum of lead time, L, and the random variable, X', drawn from a survival curve specific for the stage at the time of early detection (Figure 1C). In this screening-effect model, the possibility of patients dying during lead time is ruled out, and the possibility of dying before the expected time of dying had patients not been screened is substantially decreased.

In stage-shift model 2, no death from cancer is allowed before the time of death from cancer in the absence of screening. Specifically, persons whose cancers are detected by screening have a cancer-specific survival, X', which depends on the stage, age, and treatment at screen detection, but survival time starts at the time of screen detection. However, if this new survival would imply dying from cancer before the expected time of death in the absence of screening, such persons are assumed to die of cancer at the same time of death as in the absence of screening. This implies that the survival, S', after detection by screening is taken to be the maximum of the new survival, X', and the original survival, $L + X$ (Figure 1D).

We consider 2 versions of stage-shift model 2. In stage-shift model 2A, we assume that the survival at screen detection and the survival at clinical detection are independent. In stage-shift model 2B, we assume that the 2 survivals are dependent. Technically, the dependency is included by generating the survival at screen detection and the survival at clinical detection with the same random number, that is, using the same quantile from both survival functions. In stage-shift model 2, survival is truncated at the survival time as in the case that the individuals had not been screened, implying that men who would die of prostate cancer in the absence of screening can additionally benefit from the independency.

Cure Models

In the cure models, a fraction of the tumors detected by screening are cured because the tumors are treated earlier. Patients will not die of cancer if they are cured, but if they are not cured, their date and cause of death are not changed by early detection. This implies that survival S' is up to death from other causes with probability c (cure) and equals the original survival corrected for lead time, $L + X$, with probability $1 - c$ (no cure) (Figure 1E).

In this study we consider 2 cure models. In cure model 1, we assume that the cure rate (the probability of cure) is constant and we consider 2 estimates for the cure rate. The cure rate is estimated either from the ratio of long-term disease-specific survival of treated v. untreated cancer (cure model 1A) or from the mortality reductions observed in randomized trials (cure model 1B).

In cure model 2, the cure rate depends on the predicted lead time (time by which screening advances diagnosis). For this study we assume that the cure rate increases linearly with the lead time, L, for the first 5 years and that the cure rate is constant after a lead time of 5 years. Namely, for lead times less than 5 years the cure rate equals $L \times c/5$ and for lead time 5 years or more the cure rate equals c, where the parameter c is estimated by calibrating the model to mortality predictions observed in a trial. Note, however, that a nonlinear relationship can also be assumed between the cure rate and the lead time.

Comparing the Screening-Effect Models

The MISCAN prostate cancer model was used to simulate the progression of prostate cancer and screening in the ERSPC-Rotterdam.[14] Models were constructed using the different screening-effect models. The prostate cancer mortality reduction in the ERSPC-Rotterdam by follow-up year was estimated using each of these models. The prostate cancer mortality reduction was calculated as the ratio of the number of prostate cancer deaths prevented by screening and the number of prostate cancer deaths in the absence of screening. Predictions of mortality reduction at 9 years of follow-up of the ERSPC-Rotterdam were compared with the published mortality reduction of 27% at 9 years of follow-up in the overall ERSPC.[13] All results were calculated for the screened men in the core age group, men between age 55 and 69 at randomization, of the ERSPC.

The MISCAN Prostate Cancer Model

The MISCAN prostate cancer model is briefly described here. A more detailed description is available at http://cisnet.cancer.gov/prostate/profiles.html.

The MISCAN prostate cancer model is a microsimulation program that simulates the progression of cancer in individuals as a sequence of tumor states. The individual life histories are first simulated in the absence of screening. Prostate cancer may develop from no prostate cancer to a clinically diagnosed cancer through 1 or more screen-detectable preclinical stages. In each preclinical stage, a tumor may grow to the next clinical T stage (T1, impalpable; T2, palpable, confined to the prostate; and T3+, palpable, with extensions beyond the prostatic capsule), dedifferentiate to a higher Gleason score (well differentiated, 2–6; moderately differentiated, 7; and poorly differentiated, 8–10), or give rise to symptoms and be clinically diagnosed. The time spent in the current stage is generated from a Weibull distribution, where the parameters depend on the current stage. The choice of the next stage is determined by transition probabilities. In addition, there is a risk that a tumor in the local–regional stage (M0) will develop into distant disease (M1). The transition from the local–regional stage to the distant disease is modeled by a stage- and Gleason score-specific hazard function. The model thus includes 18 detectable preclinical states that are derived from combinations of clinical T stages, Gleason scores, and metastatic stages.

The parameters of the progression of prostate cancer were estimated by constructing models for the ERSPC-Rotterdam and calibrating the model to observed data/baseline incidence (1991) and stage distribution (IKR92/93) in The Netherlands; incidence, Gleason, and stage distributions in the control arm; and detection rates, interval cancer rates, Gleason, and stage distributions in the screen arm. Note that the parameters of the progression of prostate cancer before diagnosis were estimated independent of survival data. A detailed description of the model's progression component is given by Draisma and others.[14,15]

After men are clinically diagnosed with prostate cancer, treatment is assigned. The men can receive 3 treatment types: active surveillance, radical prostatectomy, and radiation therapy. The same treatment fractions have been assumed in the model as in the ERSPC-Rotterdam, depending on age, Gleason score, and clinical T stage. For the corresponding treatment, the time of death from prostate cancer is obtained using prostate cancer–specific survival curves. Bill-Axelson and others[16] estimated a relative risk of 0.65 for death from prostate cancer for men treated with radical prostatectomy compared with patients with no initial treatment (active surveillance). According to this result, we assumed that men receiving radical prostatectomy or radiation therapy have a relative risk of 0.65 compared with active surveillance for local–regional cancers and that those men receiving active surveillance experience the baseline prostate cancer survival. For distant prostate cancer it is assumed that treatment has no effect on survival, implying that irrespective of the treatment type, all men diagnosed with prostate cancer in the distant stage have a survival generated from the corresponding baseline prostate cancer–specific survival curve.

The baseline prostate cancer–specific survival curves have been estimated on the basis of SEER (Surveillance, Epidemiology and End Results) data in the pre-PSA era, specifically of cases diagnosed between 1983 and 1986. The survival curves were modeled using Poisson regression, with grade, stage, age, and treatment type as explanatory variables. To assign the prostate cancer–specific survival curves in our model we assumed that Gleason score of 7 or less corresponds to grade well/moderately differentiated and that Gleason score more than 7 corresponds to grade poor/undifferentiated.

Screening-effects are then modeled by superimposing screening on the life histories in the absence of screening. Preclinical cancers can be detected by screening, depending on the frequency and the sensitivity of the screening test for the specific preclinical state. The PSA test and subsequent biopsy are modeled as a single test. In accordance with the screening in the ERSPC-Rotterdam, it is assumed that the men in the screening arm had their first PSA test between November 1993 and December 1999 and that there were 3 screening rounds with an interval of 4 years between the screening rounds. The time of prostate cancer death for the men screen-detected with prostate cancer is determined using each of the screening-effect models described before in turn.

For each screening-effect model, the parameters and the data from which the parameter estimates are obtained are presented in Table 1. In the stage-shift models, the effect of early detection by screening is entirely determined by the stage-shift and the corresponding prostate cancer–specific survival curves.

In the cure models, the effect of early detection by screening depends on the cure rate, which has to be estimated. In cure model 1A, we estimated the cure rate based on the ratio of 20 years of prostate cancer–specific survival of treated v. untreated cancer (Table 1). The cure rate estimates were 0.33 for Gleason scores less or equal to 7 and 0.17 for Gleason scores greater than 7.

In cure model 1B and 2, the cure rate was estimated assuming in the model a mortality reduction of 27% in the ERSPC-Rotterdam after a follow-up of 9 years for men who were actually screened. The mortality reduction of 27% was observed in the overall ERSPC trial. We additionally assumed that the ratio between the cure rates given the Gleason scores is the same as in cure model 1A. For cure model 1B, the cure rate estimates were 0.42 for Gleason scores less than or equal to 7 and 0.23 for Gleason scores greater than 7. For cure model 2, the estimate for the cure parameter, c, was 0.69 for Gleason scores less or equal to 7 and 0.37 for Gleason scores greater than 7.

RESULTS

The predicted prostate cancer mortality reductions by follow-up time in the ERSPC-Rotterdam are presented in Figure 2. Stage-shift model 1 predicted a prostate cancer mortality reduction of 45% after a follow-up of 9 years. Stage-shift model 2 predicted a prostate cancer mortality reduction after a follow-up of 9 years of 63% for the model assuming that the survival at screen detection and the survival at clinical detection are independent (A) and 38% for the model assuming that the survival at screen detection and the survival at clinical detection are dependent (B). Cure model 1A, which assumes a constant cure rate based on the ratio of long-term survival of treated v. untreated cancer, gave the lowest mortality reduction of 21% after a follow-up of 9 years. Cure model 1B, which assumes a constant cure rate based on the ERSPC outcome, had a predicted prostate cancer mortality reduction of 27% after a follow-up of 9 years. Cure model 2 also had a predicted prostate cancer mortality reduction of 27% after 9 years, as this model was also calibrated to the 27% prostate cancer mortality reduction observed in the overall ERSPC. However, cure model 2, which assumes a cure rate that depends on lead time, gave lower prostate cancer mortality reductions in the years before the ninth follow-up year but higher prostate cancer mortality reduction in the following year.

Table 2 presents the lifetime probabilities of death from prostate cancer by stage at diagnosis for men with screen-detected prostate cancer. The effect of screening is shown by the reduction in the risk of death from prostate cancer when the cancer is detected earlier by screening. The effect of early detection by screening for local–regional cancers with Gleason score less or equal to 7 was larger in
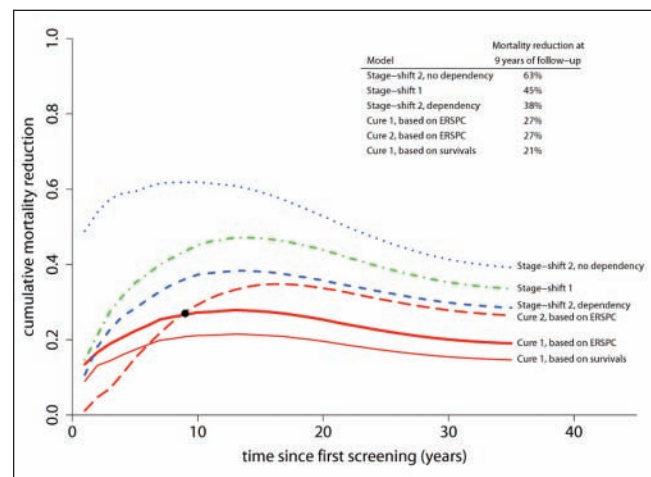

Figure 2   Predicted prostate cancer mortality reduction by follow-up time for men aged 55 to 69 at the first screening, using the different submodels for the effect of screening. The dot shows the observed 27% mortality reduction at 9 years of follow-up in the ERSPC. Stage-shift model 1: the cancer-specific survival starts after the lead time. Stage-shift model 2: the survival starts at screen detection but is taken as the maximum of the new and the original survival. Cure model 1: assuming a constant cure rate. Cure model 2: assuming a cure rate that depends on the lead time.

the stage-shift models (0.10–0.13) than in the cure models (0.05–0.09). Conversely, the effect of screening for local–regional cancers with Gleason score greater than 7 was larger in general in the cure models (0.08–0.11) than in stage-shift models 1 and 2B (0.03–0.04). Only stage-shift model 2A, in which the survival starts at screen detection but is taken as the maximum of the new and the original survival and where independence was assumed between the survival at screen detection and the survival at clinical detection, gave a larger effect (0.17) than the cure models and the other stage-shift models.

No benefit was associated with early detection by screening for cancers found in the distant stage. The relative benefit, the risk of death from prostate cancer prevented by screening compared with the risk from prostate cancer in case of no screening, was limited for cancers found in the local–regional stage with Gleason score greater than 7. However, there was a considerable relative benefit for cancers found in the local–regional stage with Gleason score less or equal to 7.

DISCUSSION

The mortality predictions for ERSPC-Rotterdam vary considerably between the stage-shift models and the cure models, which use different assumptions regarding the effect of early detection by

Table 2 Predicted Lifetime Risks of Prostate Cancer Mortality in Men Screen-Detected With Prostate Cancer by Stage and Model

		Model					
Stage at Detection	**Risk**	**SS 1**[a]	**SS 2A**[b]	**SS 2B**[c]	**Cure 1A**[d]	**Cure 1B**[e]	**Cure 2**[f]
Local–regional and Gleason score ≤7	Prostate cancer death without screening	0.14	0.14	0.14	0.14	0.14	0.14
	Prostate cancer death with screening	0.03	0.01	0.04	0.09	0.08	0.05
	Prostate cancer death prevented by screening	0.11	0.13	0.10	0.05	0.06	0.09
Local–regional and Gleason score >7	Prostate cancer death without screening	0.48	0.48	0.48	0.48	0.48	0.48
	Prostate cancer death with screening	0.44	0.31	0.45	0.40	0.37	0.38
	Prostate cancer death prevented by screening	0.04	0.17	0.03	0.08	0.11	0.10
Distant and any Gleason score	Prostate cancer death without screening	0.72	0.72	0.72	0.72	0.72	0.72
	Prostate cancer death with screening	0.72	0.72	0.72	0.72	0.72	0.72
	Prostate cancer death prevented by screening	0	0	0	0	0	0

a. Stage-shift model 1: the cancer-specific survival starts after the lead time.
b. Stage-shift model 2A: the survival starts at screen detection but is taken as the maximum of the new and the original survival, assuming no dependency between the new and original survivals.
c. Stage-shift model 2B: the survival starts at screen detection but is taken as the maximum of the new and the original survival, assuming dependency between the new and original survivals.
d. Cure model 1A; assuming a constant cure rate based on survivals.
e. Cure model 1B; assuming a constant cure rate based on the ERSPC outcome.
f. Cure model 2; assuming a cure rate that depends on the lead time and where the parameter estimate is based on ERSPC outcome.

screening. The stage-shift models predicted substantially larger prostate cancer mortality reductions than the 27% observed in the ERSPC-trial.[13]

It is likely that the best way of modeling the effect of early detection is to assign survivals that are based on observed survivals specific to screen-detected cancers and clinically diagnosed cancers. In this case, the survival for screen-detected cancers would already include both the lead time and the survival benefit because of early detection. However, these data are often not available and therefore additional assumptions that define how early detection by screening affects disease-specific survival are often needed.

The simplest version of the stage-shift model is sometimes used, for example, in models of natural history and screening of colorectal cancer.[17,18] In this simple screening-effect model, if cancers are detected earlier by screening, the survival time from the moment of screen detection is generated from a stage (at detection)–specific survival function, which is the same survival function as for men clinically detected with cancer. These survivals may lead to underestimates when the lead time is incompletely

compensated by the shift to early stages and the corresponding better survival. Colorectal cancer has a relatively short mean lead time—around 2.1 years.[19] Therefore, neglecting part of the lead time component in the survival for screen-detected colorectal cancers might not be a significant concern. However, using this simple stage-shift model in our prostate cancer study would suggest that 90% of men with screen-detected cancers would die earlier of prostate cancer than if these cancers were clinically detected. This implausible result is obtained because part of the lead time component is neglected in the survival for screen-detected cancers, whereas the mean lead time for prostate cancer is relatively long (5.4–6.9 years in the US population and 7.9 years in the ERSPC Rotterdam trial[20]).

By using additional assumptions, the stage-shift models used in this study avoid the occurrence of deaths from cancer after early detection that occur earlier than deaths from cancer if the patients were not screened and were clinically detected at a later time. Stage-shift models 1 and 2 used here have previously been used for modeling the effect of early detection by screening for breast cancer.[21,22]

In general, the use of stage-shift model 1 leads to mortality reductions that are overestimated. This is because the lead time component is overcompensated. After the lead time, men with screen-detected cancers are assigned survival specific to their stage at screen detection, even though their screen detection was some years previously. Consequently, for cancers with a large lead time and considering very few disease stages, this screening-effect model can give mortality reductions that are considerably overestimated. Because prostate cancer has a large lead time[20] and the survival considers only 4 different stages, stage-shift model 1 in this study gave prostate cancer mortality reductions that are greatly overestimated. Breast cancer, in comparison, has a relatively short lead time of 0.83 to 1.4 years,[19,23] implying that using stage-shift model 1 for modeling the effect of early detection of breast cancer might not be a significant concern.

Stage-shift model 1 was used by Etzioni and others[11] to quantify the contribution of PSA screening to the prostate cancer mortality reduction observed in the US population. They concluded that PSA screening explains 45% to 70% of the mortality decline observed in the US population by the year 2000. The results of our study show that using this screening-effect model leads to overestimated mortality reductions and, therefore, that probably less of the mortality decline can be attributed to PSA screening.

Whether using stage-shift model 2, where the survival starts at screen detection but is taken as the maximum of the new and the original survival, gives overestimates or underestimates for mortality reductions is not trivial. The magnitude of the effect of screening depends on the lead time and the survivals. In the extreme cases, cancers with short lead times and long survivals are more likely to have large predicted benefits of screening, whereas cancers with long lead times and short survivals are more likely to have small predicted benefits of screening. Therefore, whether the screening effect of the model is correct depends jointly on the lead time and the survivals. In this particular study of prostate cancer screening, the stage-shift model 2 gave mortality predictions that are overestimated.

Replicating this study for other cancers might not lead to the conclusion that the stage-shift models overestimate the effect of screening for those cancers. However, this study demonstrates that the screening-effect models should not be used without comparing the mortality predictions with observed mortality data.

In the absence of screening-trial results, the cure rate could be estimated from the ratio of long-term prostate cancer–specific survival of treated v. untreated cancer (cure model 1A). Using this cure rate estimate gave a predicted prostate cancer mortality reduction that is somewhat lower than the observed reduction in the ERSPC-trial. Estimating the cure rate (cure models 1B and 2) by calibrating the model to the observed prostate cancer mortality reduction in the overall ERSPC leads to survival benefits that result in a 27% prostate cancer mortality reduction in the ERSPC-Rotterdam. In cure model 1 we assumed a constant cure rate, and in cure model 2 we assumed a cure rate that increases with length of the lead time. It is unclear whether by using 1 of these 2 screening-effect models the mortality reduction before and after the ninth year of follow-up is modeled well. It is also unclear whether the effect of screening is modeled correctly by stage at diagnosis (Table 2). In this study we assumed an increasing cure rate for the lead time years 1 to 5; however, we could have also assumed a different relationship between the cure rate and the lead time. For example, we could have assumed that the cure rate increases slowly for long lead times and faster for shorter lead times. However, because mortality reductions before and after the ninth year of follow-up are not yet available, it is not possible to validate the cure models completely.

In our models, the parameters of the progression of prostate cancer up to clinical diagnosis and screen detection were estimated first and the cure parameter was estimated subsequently. With sufficient follow-up data of screen-detected and clinically diagnosed patients, it would be useful to estimate these parameters jointly by calibrating the model to observed incidence data, detection rates, and mortality data.

A limitation of this study is that we predicted prostate cancer mortality reduction in the ERSPC-Rotterdam and compared it with the observed 27% prostate cancer mortality reduction in the overall ERSPC and not with the one observed in the ERSPC-Rotterdam. However, we do not expect the reduction in prostate cancer mortality in the ERSPC-Rotterdam to be very different, as according to the results of the ERSPC trial the rate ratio for death from prostate cancer changes very little when the Rotterdam section is excluded from the ERSPC.[13]

In conclusion, different screening-effect models can be used to model the effect of screening, and these different models gave different outcomes in this study. The first message of this study is that it is important to make explicit what assumptions are

made about the effect of early detection by screening on survival. The second message is that trial data are essential for the validation of the screening-effect models. The advantage of the cure model is that the cure parameter could be calibrated to the observed 27% prostate cancer mortality reduction in the ERSPC-trial. Using the stage-shift models to include the effect of screening considerably overestimated the mortality reduction. Therefore, the third message is that stage-shift models should be used with care when modeling the effect of screening of cancers with long lead times, such as prostate cancer.

REFERENCES

1. Smith RA, Cokkinides V, Brooks D, Saslow D, Brawley OW. Cancer screening in the United States, 2010: a review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin. 2010;60:99–119.

2. Breen N, Wagener DK, Brown ML, Davis WW, Ballard-Barbash R. Progress in cancer screening over a decade: results of cancer screening from the 1987, 1992, and 1998 National Health Interview Surveys. J Natl Cancer Inst. 2001;93:1704–13.

3. Benson VS, Patnick J, Davies AK, Nadel MR, Smith RA, Atkin WS. Colorectal cancer screening: a comparison of 35 initiatives in 17 countries. Int J Cancer. 2008;122:1357–67.

4. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986–2005. J Natl Cancer Inst. 2009;101:1325–9.

5. de Gelder R, Bulliard JL, de Wolf C, Fracheboud J, Draisma G, Schopper D, et al. Cost-effectiveness of opportunistic versus organised mammography screening in Switzerland. Eur J Cancer. 2009;45:127–38.

6. Mandelblatt JS, Cronin KA, Bailey S, Berry DA, de Koning HJ, Draisma G, et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. Ann Intern Med. 2009;151:738–47.

7. Mandelblatt JS, Lawrence WF, Womack SM, Jacobson D, Yi B, Hwang YT, et al. Benefits and costs of using HPV testing to screen for cervical cancer. JAMA. 2002;287:2372–81.

8. van den Akker-van Marle ME, van Ballegooijen M, van Oortmarssen GJ, Boer R, Habbema JD. Cost-effectiveness of cervical cancer screening: comparison of screening policies. J Natl Cancer Inst. 2002;94:193–204.

9. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Boer R, Wilschut J, Habbema JD. At what costs will screening with CT colonography be competitive? A cost-effectiveness approach. Int J Cancer. 2009;124:1161–8.

10. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149:659–69.

11. Etzioni R, Tsodikov A, Mariotto A, Szabo A, Falcon S, Wegelin J, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. Cancer Causes Control. 2008;19:175–81.

12. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005;353:1784–92.

13. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009;360:1320–8.

14. Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, Schroder FH, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst. 2003;95:868–78.

15. Draisma G, Postma R, Schroder FH, van der Kwast TH, de Koning HJ. Gleason score, age and screening: modeling dedifferentiation in prostate cancer. Int J Cancer. 2006;119:2366–71.

16. Bill-Axelson A, Holmberg L, Filen F, Ruutu M, Garmo H, Busch C, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. J Natl Cancer Inst. 2008;100:1144–54.

17. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. JAMA. 2000;284:1954–61.

18. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Habbema JD, Kuipers EJ. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. J Natl Cancer Inst. 2009;101:1412–22.

19. Wu D, Rosner GL, Broemeling LD. Bayesian inference for the lead time in periodic cancer screening. Biometrics. 2007;63: 873–80.

20. Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst. 2009;101:374–83.

21. Mandelblatt J, Schechter CB, Lawrence W, Yi B, Cullen J. The SPECTRUM population model of the impact of screening and treatment on U.S. breast cancer trends from 1975 to 2000: principles and practice of the model methods. J Natl Cancer Inst Monogr. 2006;(36):47–55.

22. Plevritis SK, Sigal BM, Salzman P, Rosenberg J, Glynn P. A stochastic simulation model of U.S. breast cancer mortality trends from 1975 to 2000. J Natl Cancer Inst Monogr. 2006;(36):86–95.

23. Chen Y, Brock G, Wu D. Estimating key parameters in periodic breast cancer screening-application to the Canadian National Breast Screening Study data. Cancer Epidemiol. 2010;34:429–33.