Chapter 4

How does early detection by screening affect disease progression? Modeling estimated benefits in prostate cancer screening

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ABSTRACT

Background

Simulation models are essential tools for estimating benefits of cancer screening programs. Such models include a screening-effect model which 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 due to earlier detection, and the cure model, where early detection enhances the chances of cure from disease. The objective of this paper is to describe the commonly used screening-effect models and analyze their predicted mortality benefit in a model for prostate cancer screening.

Methods

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 in ERSPC-Rotterdam were calculated. We compared four 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 nine years reductions in prostate cancer mortality varying from 38% to 63% for ERSPC-Rotterdam compared with a 27% observed in the overall 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. Using the stage-shift models to include the effect of screening considerably over-estimated 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.

INTRODUCTION

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 (FOBT), 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 US.[4] Death from cancer might be postponed or prevented if a cancer is found earlier as 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 for explaining observed trends in cancer incidence and mortality. For example Etzioni et al.[11] used two 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 due to screening. Also, Berry et al.[12] showed with seven 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 on how diagnosing and treating patients at a less advanced stage affects prostate cancer mortality. Screening-effect models may be summarized generally into two 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, i.e. 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 paper 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 4.1, Panel B). In the absence of screening, the time of prostate

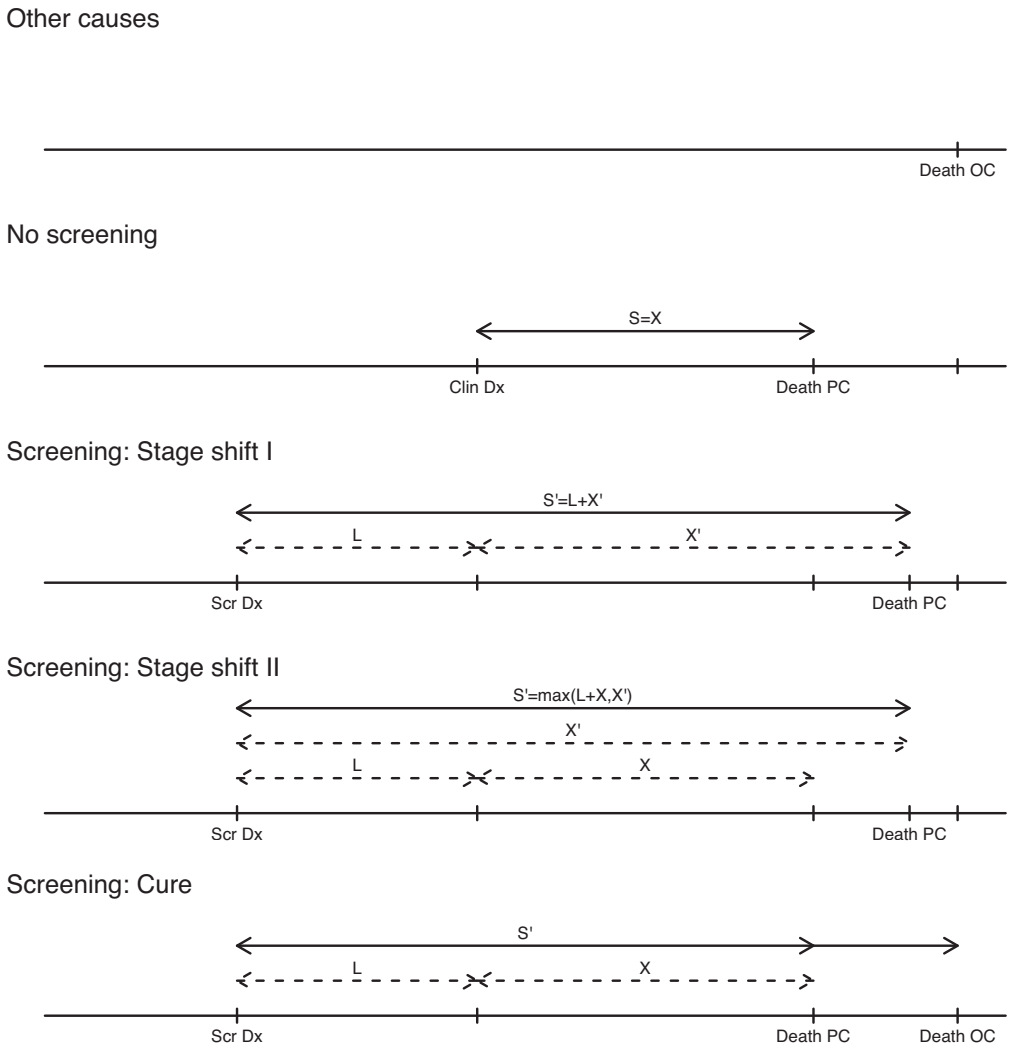

Figure 4.1: Modeling the impact of early detection on disease progression. Each panel shows relevant events in an individual life history on a time line. Panel A indicates the time of death from other causes than prostate cancer (Death OC). Panel B presents the prostate cancer history in the absence 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 to E illustrate the impact of early detection by screening in the various models. Panel 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. Panel 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'*. Panel 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).

cancer death is defined by survival, *S*, after clinical diagnosis which equals a random 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 sub-model that takes into account that persons diagnosed with cancer early by screening may have a better cancer-specific survival compared to 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 four different screening-effect models: two stage-shift models and two cure models. Figure 4.1 illustrates the different models in Panel C to E, and Table 4.1 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

Table 4.1: Parameters and data source for each screening-effect model.

Model	Parameters	Parameter value by stage at diagnosis			Source
		Local/Regional Gleason score <=7	Local/Regional Gleason score >7	Distant Any Gleason score	
Stage-shift 1, 2A, 2B	Stage specific survival at*				SEER prostate-cancer-specific survival in pre PSA era (1983-1986) with hazard ratio 0.65 from Bill-Axelson et al.[14]
	5 year	0.98	0.73	No effect (0.45)*	
	10 year	0.90	0.49	No effect (0.29)*	
Cure 1A	Stage specific probability of cure	0.33	0.17	No effect	Ratio of long term prostate-cancer-specific survival of non-treated and treated prostate cancer in pre-PSA era (SEER 1983-1986) with hazard ratio 0.65 from Bill-Axelson et al.[14] (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 nine 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 27% observed mortality reduction in ERSPC at nine years of follow-up.[13]

*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.

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' live 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 employ an additional assumption to avoid implausible results of reduced life-expectancy with screening. In this study we consider the following two stage-shift models.

In *Stage-shift model 1* no death from cancer is allowed during lead time, i.e. 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*, i.e. 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 4.1, Panel C). 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 4.1, Panel D).

We consider two 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 two 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, i.e. 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 4.1, Panel E).

In this study we consider two cure models. In *Cure model 1* we assume that the cure rate (the probability of cure) is constant and we consider two estimates for the cure rate. The cure rate is either estimated from the ratio of long term disease specific survival of treated versus 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 < 5 years the cure rate = $L \times c/5$ and for lead time ≥ 5 years cure rate = *c*, where the parameter *c* is estimated by calibrating the model to mortality predictions observed in a trial. Note however that a non-linear 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.[15] 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 nine years of follow-up of the ERSPC-Rotterdam were compared to the published mortality reduction of 27% at nine 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 micro-simulation program which 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 one 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 become 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 grade-specific hazard function. The model thus includes 18 detectable preclinical states that are derived from combinations of clinical T-stages, differentiation grades, 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 et al.[15-16]

After men are clinically diagnosed with prostate cancer, treatment is assigned. The men can receive three 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 et al.[14] estimated a relative risk of 0.65 for death from prostate cancer for men treated with radical prostatectomy compared to 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 to 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 (prostate-specific antigen) 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 may 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 a time-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 4.1. 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 prostate-cancer-specific survival of treated versus untreated cancer (Table 4.1). 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-trial Rotterdam after a follow-up of nine 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 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 4.2. *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 versus 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

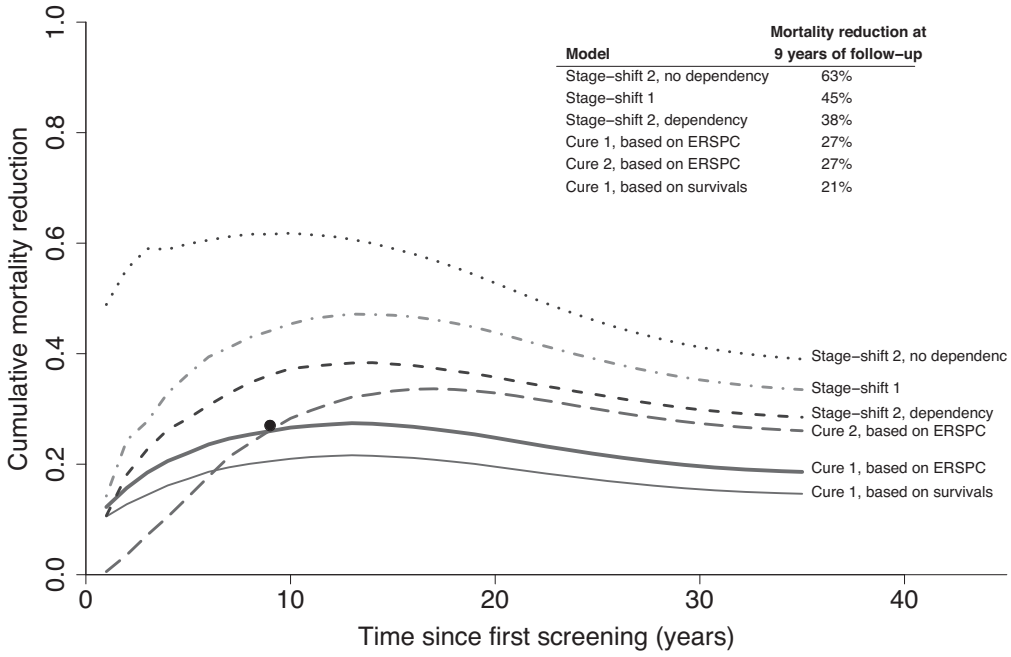

Figure 4.2: Predicted prostate cancer mortality reduction by follow-up time for men aged 55-69 at the first screening, using the different sub-models for the effect of screening. The dot shows the observed 27% mortality reduction at nine years of follow-up in the ERSPC. *Stage-shift model 1*: the cancer-specific 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.

cure rate that depends on lead time gave lower prostate cancer mortality reductions in the years before the 9th follow-up year but higher prostate cancer mortality reduction in the following year.

Table 4.2 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 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 model 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 to 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.

Table 4.2: 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*	SS 2A†	SS 2B‡	Cure 1A§	Cure 1B‖	Cure 2¶
Local/regional and Gleason score <= 7	Death from prostate cancer without screening	0.14	0.14	0.14	0.14	0.14	0.14
	Death from prostate cancer with screening	0.03	0.01	0.04	0.09	0.08	0.05
	Death from prostate cancer prevented by screening	0.11	0.13	0.10	0.05	0.06	0.09
Local/regional and Gleason score > 7	Death from prostate cancer without screening	0.48	0.48	0.48	0.48	0.48	0.48
	Death from prostate cancer with screening	0.44	0.31	0.45	0.40	0.37	0.38
	Death from prostate cancer prevented by screening	0.04	0.17	0.03	0.08	0.11	0.10
Distant and any Gleason score	Death from prostate cancer without screening	0.72	0.72	0.72	0.72	0.72	0.72
	Death from prostate cancer with screening	0.72	0.72	0.72	0.72	0.72	0.72
	Death from prostate cancer prevented by screening	0.00	0.00	0.00	0.00	0.00	0.00

*SS 1: Stage-shift model 1, the cancer-specific survival starts after the lead time.
†SS 2A: 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.
‡SS 2B: 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.
§Cure 1A: Cure model, assuming a constant cure rate based on survivals.
||Cure 1B: Cure model, assuming a constant cure rate based on the ERSPC outcome.
¶Cure 2: Cure model, assuming a cure rate that depends on the lead time and where the parameter estimate is based on ERSPC outcome.

DISCUSSION

The mortality predictions for ERSPC-Rotterdam vary considerably between the stage-shift models and the cure models, which employ different assumptions regarding the effect of early detection by 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 under-estimates 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 of 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, while 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 employing additional assumptions, the stage-shift models used in this study avoid the occurrence of deaths from cancer after early detection which occurs 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 over-estimated. This is because the lead time component is over-compensated. 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 over-estimated. Since 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 over-estimated. Breast cancer on the other hand has a relatively short lead time of 0.83-1.4 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.

Etzioni et al.[11] used in two models *Stage-shift model 1* 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 over-estimated mortality reductions and that therefore 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 over-estimates or under-estimates 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 over-estimated.

Replicating this study for other cancers might not lead to the conclusion that the stage-shift models over-estimate 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 versus 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 model 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 one of these two 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 4.2). 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, since 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 over-estimated 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.

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Effects of Prostate Cancer Screening and Treatment

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