Original Article

The Efficacy of Prostate-Specific Antigen Screening: Impact of Key Components in the ERSPC and PLCO Trials

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BACKGROUND: The European Randomized Study of Screening for Prostate Cancer (ERSPC) demonstrated that prostate-specific antigen (PSA) screening significantly reduced prostate cancer mortality (rate ratio, 0.79; 95% confidence interval, 0.69-0.91). The US Prostate, Lung, Colorectal, and Ovarian (PLCO) trial indicated no such reduction but had a wide 95% CI (rate ratio for prostate cancer mortality, 1.09; 95% CI, 0.87-1.36). Standard meta-analyses are unable to account for key differences between the trials that can impact the estimated effects of screening and the trials' point estimates. **METHODS:** The authors calibrated 2 microsimulation models to individual-level incidence and mortality data from 238,936 men participating in the ERSPC and PLCO trials. A cure parameter for the underlying efficacy of screening was estimated by the models separately for each trial. The authors changed step-by-step major known differences in trial settings, including enrollment and attendance patterns, screening intervals, PSA thresholds, biopsy receipt, control arm contamination, and primary treatment, to reflect a more ideal protocol situation and differences between the trials. **RESULTS:** Using the cure parameter estimated for the ERSPC, the models projected 19% to 21% and 6% to 8%, respectively, prostate cancer mortality reductions in the ERSPC and PLCO settings. Using this cure parameter, the models projected a reduction of 37% to 43% under annual screening with 100% attendance and biopsy compliance and no contamination. The cure parameter estimated for the PLCO trial was 0. **CONCLUSIONS:** The observed cancer mortality reduction in screening trials appears to be highly sensitive to trial protocol and practice settings. Accounting for these differences, the efficacy of PSA screening in the PLCO setting is not necessarily inconsistent with ERSPC results. ***Cancer*** **2018;124:1197-206.** *© 2017 American Cancer Society.*

KEYWORDS: modeling, mortality reduction, prostate cancer, prostate-specific antigen (PSA) screening.

INTRODUCTION

The European Randomized Study of Screening for Prostate Cancer (ERSPC)[1-3] demonstrated a significant prostate cancer mortality reduction of 21% for the prostate-specific antigen (PSA) screening arm, whereas the US-based Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial did not demonstrate a difference in prostate cancer mortality between the arms but had wide 95% confidence intervals (95% CIs) (prostate cancer mortality rate ratio, 1.09; 95% CI, 0.87-1.36).[4] Several explanations for these seemingly inconsistent results have been debated.[5-8]

Selective trial populations and different protocols and practice settings, including differences in pre-trial screening, receipt of biopsies, control arm contamination, and primary treatments, may have influenced the trial results.

The ERSPC trial was conducted in 7 centers in Europe with 162,243 men aged 55 to 69 years at the time of randomization. PSA testing was not common at the start of the trial and the estimated contamination in the control arm was <15%.[7] The majority of centers used a screening interval of 4 years and a PSA threshold of 3.0 ng/mL for biopsy referral.

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Approximately 86% of the positive screens were followed by a biopsy.[1] The PLCO trial was conducted among 76,693 men aged 55 to 74 years, among whom prior screening already was common. At least 45% of the participants had undergone ≥1 PSA test before randomization.[4] In addition, participants in the control arm were screened on average 2.7 times during the 6-year intervention phase of the trial.[9] Annual screening was used and the threshold for a positive PSA test was 4.0 ng/mL. Because in this trial the biopsies were performed outside the study, only approximately 35% of participants with a positive screen received a biopsy.[10] Both trials involved variable use of digital rectal examination.

Because of these differences, the results of the trials are not directly comparable. In standard meta-analyses, the results simply were pooled,[11-13] suggesting that PSA screening has little effect on prostate cancer mortality. To the best of our knowledge, possible reasons for the apparent lack of consistency between the trials have not been evaluated formally to determine their quantitative impact on observed mortality reductions.

The objective of the current study was to estimate the impact of trial population, protocols, contamination, and practice settings on the observed prostate cancer mortality reduction. We used 2 independently designed natural history models, which were informed using individual-level data from both trials, to systematically investigate the impact of these characteristics on the estimated efficacy of PSA screening.

MATERIALS AND METHODS

Data

Individual data from both the ERSPC trial and the PLCO trial were obtained regarding age at randomization, trial arm, screening center, screening test dates and results, performance of biopsy, prostate cancer incidence, mode of detection (screen or interval cancer), clinical TNM stage and Gleason score at the time of diagnosis, primary treatment, and date and cause of death. The median follow-up was 11 years for the ERSPC trial[2] and 13 years for the PLCO trial.[4]

Modeling the Trials

Two multistate disease course models of the Cancer Intervention and Surveillance Modeling Network (CISNET), the Erasmus Medical Center-MIcrosimulation Screening Analysis (Erasmus-MISCAN) model, and the Fred Hutchinson Cancer Research Center (FHCRC) model were used to simulate the trials. The models were independently developed to describe the natural history of prostate cancer and to investigate prostate cancer progression, screening sensitivity, detection, and improvement in prognosis given screening and primary treatment. The 2 models have been described extensively (https://resources.cisnet.cancer.gov/registry).[14-17] In short, in the Erasmus-MISCAN model, disease progresses through a sequence of states defined by stage and grade. In each state, there is a probability of clinical detection and, depending on the screen sensitivity and attendance, a probability of screen detection.[17,18] In the FHCRC model, PSA growth is estimated externally using the results of serial PSA tests from the Prostate Cancer Prevention Trial. The risk of onset of a preclinical screen-detectable tumor increases with age and the risks of progression to metastasis and of disease detection in the absence of screening increases with PSA levels.[15] Detailed descriptions of the models are provided in Supporting Information Material 1.

Calibration

Each model was calibrated to the ERSPC and PLCO trials separately. Disease progression rates (for the Erasmus-MISCAN model as well as the PSA test sensitivity) were calibrated against the incidence and stage distributions of clinically detected cancers in both control arms and the screen-detected and interval cancers in the screened arms (see Supporting Information Material 2). We used enrollment patterns, screen attendance, and receipt of biopsy by age and PSA level to model the number of screens and biopsies in the screened arms of the trials (Table 1).[9] Screening before, during, and after the intervention period (contamination) in the PLCO trial was simulated using a model described previously.[19] Briefly, we assumed that before the trial, participants followed screening patterns previously reconstructed for the US population,[20] which they also followed after the 6-year intervention phase. We assumed control arm participants had a 20% higher intensity of screening than the general US population during the 6-year invention period to match the estimated average of 2.7 screens in this period.[9] For the ERSPC trial, we assumed a contamination rate of 5% of US population screening patterns, leading to a comparable number of screened men as estimated in several centers.[21-23]

Survival

Both models generated prostate cancer survival from the time of clinical diagnosis in the absence of screening or localized treatment benefits. Prostate cancer survival was estimated using a common proportional hazards regression model with piecewise constant hazards[24] fit to

TABLE 1. Inputs of the Models for Each Trial[a]

	ERSPC		PLCO	
	Screen Arm	Control Arm	Screen Arm	Control Arm
Sample size	72,891	89,352	38,343	38,350
Patient age at randomization, y	55-69	55-69	55-74	55-74
Screen attendance	Average: 82% MISCAN: By center and round FHCRC: By center	NA	By age and round Average: 85%	NA
Screen protocol	2-y interval for Sweden, 4 y for other centers (7-y interval between rounds 1 and 2 for Belgium) Screening from age 55 y to 69/71/74 y depending on center MISCAN: PSA threshold of 3 ng/mL for all centers FHCRC: PSA threshold and DRE testing by center	NA	1-y interval for 6 y; PSA threshold of 4 ng/mL Screening from ages 55-74 y FHCRC: also DRE testing	NA
Biopsy compliance	Average: 86% MISCAN: By age, center, and round FHCRC: By age, PSA, and center	Average: 86% MISCAN: 86% for all FHCRC: By age, PSA, and center	By age and round; average of 35% FHCRC: also by PSA	Average: 35%
Biopsy sensitivity	80%	80%	Increasing from 70% in 1990 to 93% in 2000	Increasing from 70% in 1990 to 93% in 2000
Contamination	Pretrial screening: approximately 3%-5% of participants had a PSA test No contamination during trial	Pretrial screening: approximately 3%-5% of participants had a PSA test During trial: approximately 17,000 tests	Pretrial screening: approximately 50% of participants had a PSA test During trial: no contamination Posttrial screening: US population screening	Pretrial screening: approximately 50% of participants had a PSA test During trial: approximately 2.7 tests per participant [9] Posttrial screening: US population screening
Treatment of locoregional cases	By age, stage, and grade, on average 47% radical prostatectomy[b] 21% radiotherapy 32% conservative management or active surveillance	By age, stage, and grade, on average 53% radical prostatectomy[b] 17% radiotherapy 30% conservative management or active surveillance	By age, stage, and grade, on average 59% radical prostatectomy[b] 22% radiotherapy 19% conservative management or active surveillance	By age, stage, and grade, on average 58% radical prostatectomy[b] 22% radiotherapy 20% conservative management or active surveillance
Life tables	MISCAN: by European country (Human Mortality Database) FHCRC: US life tables (Berkeley Mortality Database)	MISCAN: by European country (Human Mortality Database) FHCRC: US life tables (Berkeley Mortality Database)	US life tables (Berkeley Mortality Database)	US life tables (Berkeley Mortality Database)

Abbreviations: DRE, digital rectal examination; ERSPC, European Randomized Study of Screening for Prostate Cancer; FHCRC, Fred Hutchinson Cancer Research Center; MISCAN, Erasmus Medical Center-MIcrosimulation Screening Analysis; NA, not applicable; PLCO, Prostate, Lung, Colorectal, and Ovarian; PSA, prostate-specific antigen.

[a] The majority of inputs were age-specific, stage-specific, and/or center-specific. The average value is presented for comparison between the arms and trials.

[b] This category included radical prostatectomy, radical prostatectomy with hormone therapy, and radiotherapy with hormone therapy, all of which were assumed to have a hazard ratio of 0.62 on prostate cancer death.

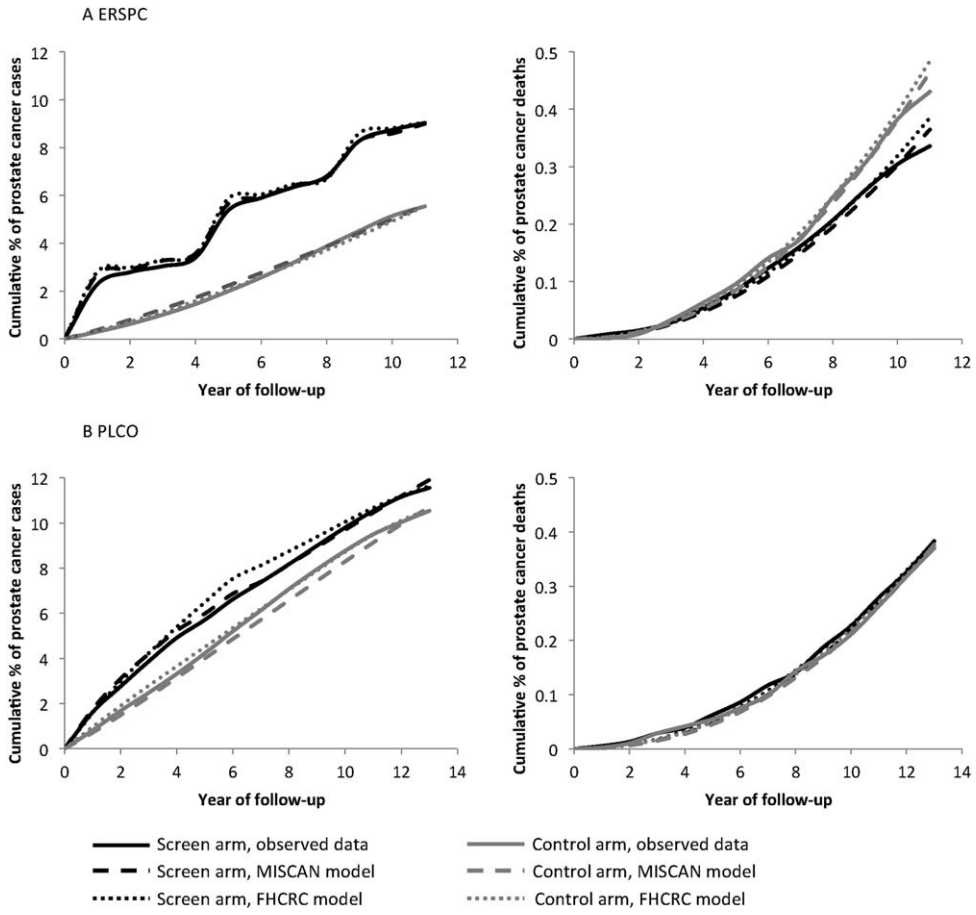

Figure 1. Observed and predicted cumulative percentage of (*Left*) prostate cancer incidence and (*Right*) prostate cancer mortality in the (A) European Randomized Study of Screening for Prostate Cancer (ERSPC) trial and (B) Prostate, Lung, Colorectal, and Ovarian (PLCO) trial by year of follow-up. FHCRC indicates Fred Hutchinson Cancer Research Center; MISCAN, Erasmus Medical Center-MIcrosimulation Screening Analysis.

Surveillance, Epidemiology, and End Results data for untreated cases diagnosed between 1983 and 1986, just before the advent of PSA screening. This baseline survival was improved for patients with localized disease who underwent radical prostatectomy or radiotherapy in combination with hormone therapy, using a hazard ratio (HR) of 0.62 and for patients with nonmetastatic disease who received radiation monotherapy using an HR of 0.7.[25] Distributions of treatments depending on age, Gleason score, and stage of disease were based on separate multinomial regression models fit to trial data (see Supporting Information Material 3). Other-cause survival was generated using US and European life tables.

Modeling Screening Benefit

The mortality benefit of PSA screening was modeled as a cure probability that depended on the lead time (years by which detection of the cancer is advanced by screening compared with the clinical situation) and was implemented only for screen-detected, nonmetastatic, and non-overdiagnosed cases as cure probability = 1 - exp (-cure parameter × lead time). Thus the probability of cure increases with lead time, with a diminishing incremental benefit for longer lead times. In the models, cured men were assigned to die at their independently generated date of other-cause death. Men who were not cured died at the same time they would have died if they had not been screened.

In a previous study modeling the PLCO trial, the models substantially overprojected observed prostate cancer mortality despite closely reproducing incidence and stage and grade patterns.[19] Therefore, we included a baseline survival HR to improve the baseline survival, reasoning that there have been improvements in disease management since the period between 1983 and 1986 beyond screening or primary treatment. In the current study, we jointly

calibrated this HR with the cure parameter to the observed prostate cancer mortality data for both trials separately.

Model Runs

Each model projected the mortality rate ratio for each trial by year of follow-up. Then, using the cure parameter calibrated to the ERSPC (because the published effect of screening was positive), the models systematically varied key characteristics of the trials. We first replaced observed characteristics (control arm contamination, attendance patterns, receipt of biopsies) in the ERSPC setting in a cumulative way with idealized versions of no control arm contamination, perfect attendance, and perfect compliance with biopsy recommendations; then substituted the idealized ERSPC setting with the idealized PLCO setting; and finally inserted observed PLCO characteristics (see Supporting Information Material 4). In each run, the numbers of prostate cancer cases and prostate cancer deaths and corresponding person-years of follow-up were projected, and the prostate mortality rate ratio was calculated. We quantified stochastic uncertainty around mortality rate ratio point estimates using ranges across 100 simulations and examined sensitivity to estimates of the cure parameter.

RESULTS

Calibration Results

Both calibrated models approximated the observed patterns of prostate cancer incidence, grade and stage distributions, and mortality in both arms of both trials (Fig. 1) (see Supporting Information Materials 5 and 6). The corresponding lead times are shown in Figure 2 for men aged 60 to 65 years at the time of screen detection and in Supporting Information Material 7 for all age groups. The estimated cure parameter was 0.22 (Erasmus-MISCAN) and 0.18 (FHCRC) for the ERSPC. The corresponding cure probability by lead time is shown in Figure 3. Cancers detected early by screening were detected substantially earlier in both trials. For the PLCO trial, we estimated HRs to improve baseline survival of 0.40 (Erasmus-MISCAN) and 0.31 (FHCRC) and HRs for the ERSPC of 0.82 (Erasmus-MISCAN) and 0.77 (FHCRC), illustrating important differences in background risk for men enrolled in the 2 trials. Because there were more prostate cancer deaths in the screening arm compared with in the control arm of the PLCO trial, the estimated cure parameter for that trial was 0 for both models. Consequently, we examined the sensitivity of the mortality reduction and PSA screening efficacy to trial population, protocols, and practice settings using the cure parameter estimated for the ERSPC.

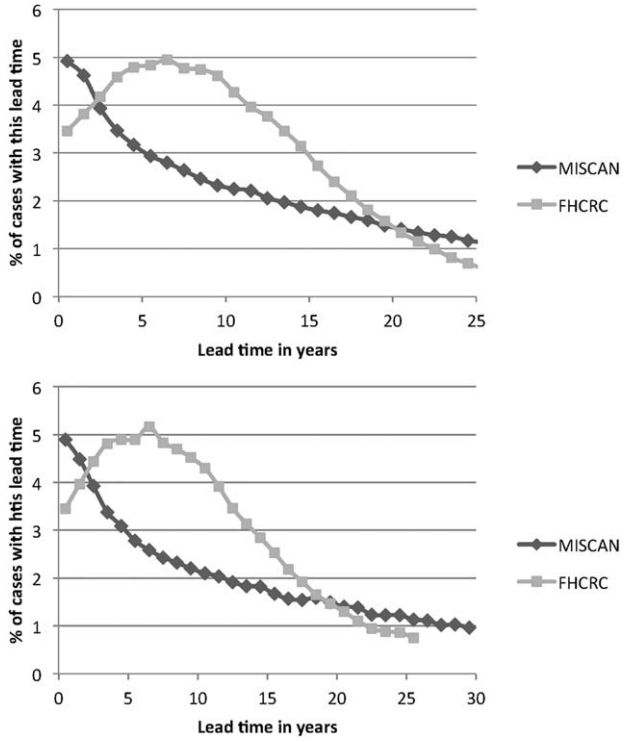

Figure 2. Lead time distribution of screen-detected cases in the models using (A) the base European Randomized Study of Screening for Prostate Cancer (ERSPC) model or (B) the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial model for men aged 60 to 65 years at the time of prostate cancer diagnosis. This is defined as the time from detection (screen and interval) until clinical detection before age 100 years in the absence of death from other causes. In the Erasmus Medical Center-MIcrosimulation Screening Analysis (Erasmus-MISCAN) and Fred Hutchinson Cancer Research Center (FHCRC) models, approximately 31% and 20%, respectively, of cases were clinically detected and therefore had a lead time of 0 (and a corresponding cure probability of 0). Results for other ages at the time of diagnosis were found to be similar.

Prostate Cancer Mortality Reduction Adjusted for Different Trial Characteristics

Starting with the observed prostate cancer mortality reduction in the ERSPC trial of 21% (95% CI, 9%-32%) after 11 years of follow-up (run 0: 21% in Erasmus-MISCAN and 19% in FHCRC), the projected mortality reduction increased as the settings became more idealized (Fig. 4). The largest screening effect in ERSPC was predicted under no contamination, 100% attendance, 100% receipt of biopsy for positive screens, and annual screening, with mortality reductions of 43% (Erasmus-MISCAN; uncertainty range, 34%-52%) and 37% (FHCRC; uncertainty range, 16%-59%) after 11 years of follow-up (run 5). Sensitivity analyses using the 95% CI of the point estimate of the ERSPC for fitting the cure parameter indicated a prostate cancer mortality reduction of 20% to 64% in run 5 (see Supporting

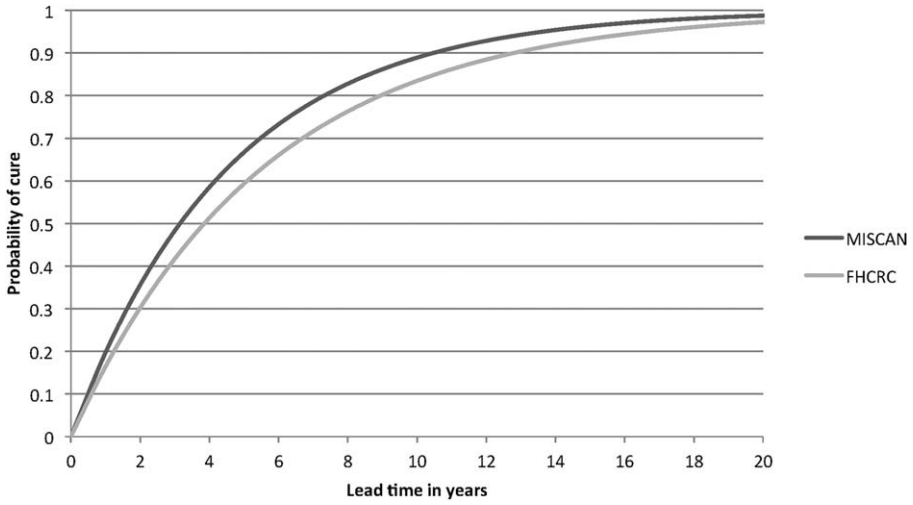

Figure 3. The cure probability for screen-detected cases by lead time in the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial as estimated by the 2 models. In the models, cured men were assigned to die at their independently generated date of other-cause death. Men who were not cured died at the same time they would have died if they had not been screened. Therefore, for example, 60% (Fred Hutchinson Cancer Research Center [FHCRC]) to 70% (Erasmus Medical Center-MIcrosimulation Screening Analysis [Erasmus-MISCAN]) of men with a lead time of 5 years will not die of prostate cancer and the remaining 30% to 40% will die at the same time and from the same cause as if they had not been screened.

Information Material 8). Sensitivity analyses of uncertainty in the joint estimation of the cure parameter and improvement in baseline prostate cancer survival indicated a prostate cancer mortality reduction of 16% to 65% in run 5 (see Supporting Information Material 9).

The projected reduction diminished substantially as the idealized PLCO setting was systematically replaced with observed characteristics to 8% (Erasmus-MISCAN) and 6% (FHCRC) under observed settings for all characteristics after 13 years of follow-up (run 12). These projections approach the published ratio in PLCO (9% increase; 95% CI, 13% reduction to 36% increase). When a cure parameter of 0 was used, an increase in prostate cancer mortality was found (run 13: 3% in Erasmus-MISCAN and 5% in FHCRC). Both models found that infrequent receipt of biopsies (runs 9 vs 10) and high contamination (runs 11 vs 12) increased the prostate cancer mortality rate ratio considerably. Although the models generally agreed, different effects were predicted for some trial characteristics, especially for 100% receipt of biopsy in the ERSPC trial and for the PSA threshold of 4 ng/mL in the PLCO trial.

DISCUSSION

Efficacy is the extent to which a specific intervention produces a beneficial result under ideal conditions. In practice, true efficacy rarely is estimated as such. Randomized controlled trials, the gold standard for assessing screening interventions, can only assess efficacy limited by the circumstances of the implementation. The results of the current study indicate that, by explicitly accounting for differences in implementation and settings between the ERSPC and PLCO trials, it is possible to partially reconcile their seemingly different results. In particular, the infrequent receipt of biopsies after a positive test and the high contamination rate in the control arm of the PLCO trial are the main factors explaining why, even in the presence of a screening benefit such as that observed in the ERSPC trial, the PLCO trial could have yielded a negative result.

In addition to allowing us to examine differences between the trials, the models also afforded insights into the mortality benefit that might potentially result from an ideal screening regimen. If all men in the ERSPC trial were screened annually (ignoring selection effects), received a biopsy after a positive test, and there was no contamination, the models predicted that the prostate cancer mortality reduction due to screening would have been approximately 40% after 11 years. Extrapolating this to the European population setting suggests that 1 screen at age 55 years could lead to 6657 (5%) fewer prostate cancer deaths annually and biennial screening for patients aged 55 to 69 years could lead to 62,529 (44%) fewer deaths annually (see Supporting Information Material 10).

Earlier studies investigated explanations for the apparently different results of the ERSPC and PLCO

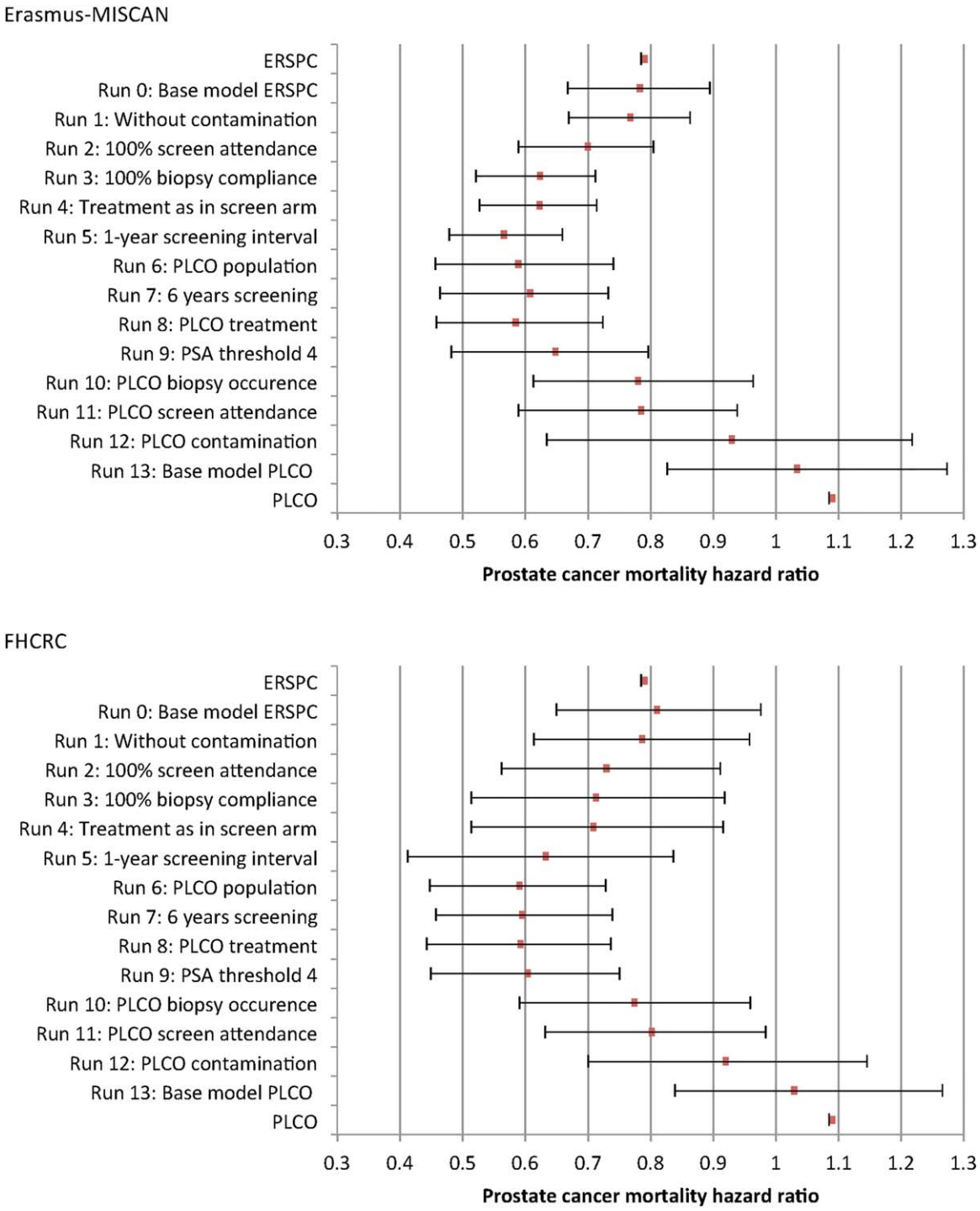

Figure 4. Step-by-step prostate cancer mortality rate ratios and simulation-based uncertainty ranges for the Erasmus Medical Center-MIcrosimulation Screening Analysis (Erasmus-MISCAN) and Fred Hutchinson Cancer Research Center (FHCRC) models. The changes in the models are cumulative. In run 13, a cure parameter of 0 was used; in all other runs, the European Randomized Study of Screening for Prostate Cancer (ERSPC)-based cure parameter was used (0.22 for MISCAN and 0.18 for FHCRC). Supporting Information Material 9 provides intervals that incorporate variability in the estimated cure rate parameter (FHCRC model). For each run of 0 to 13, 100 simulations of a single ERSPC or Prostate, Lung, Colorectal, and Ovarian (PLCO) trial population were performed to generate sample mortality rate ratios; the bracketed line (uncertainty range) and dot represent, respectively, the range and mean of the sample mortality rate ratios observed over the 100 simulations. In runs 0 to 5 a follow-up of 11 years was used, whereas in runs 6 to 13 the follow-up was 13 years. In each step, the listed implementation change was added to the previous step. PSA indicates prostate-specific antigen.

trials.[7,26-28] We previously found that contamination in the PLCO trial substantially lowered its power.[19] Questions have been raised about possible differences in the treatment men received in the screening and control arms of the ERSPC trial.[29] However, after correcting for age and tumor stage, no significant differences in treatment were found.[30] The results of the current analysis demonstrate that, if all patients in the control arm received treatment according to the frequencies (by age and tumor stage and grade) observed in the screening arm, the prostate cancer mortality reduction would remain unchanged. A similar result holds in the PLCO trial.

To the best of our knowledge the level of contamination in the ERSPC trial has not been systematically reported and therefore had to be estimated from earlier published studies, which demonstrated contamination ranging from 7% to 40% per year across centers.[21-23,31] To our knowledge, the only study to investigate the level of screening before the start of the ERSPC trial is a study of the Finnish center.[22] In this study, approximately 10% of the men in the intervention arm had been screened before. However, both pre-trial and contamination estimates included PSA tests conducted because of symptoms, which could have accounted for up to one-half of the PSA tests performed.[21,23] In addition, not all PSA tests were followed by a biopsy. For example, in the Rotterdam control arm, only 8% of positive opportunistic PSA tests were followed by biopsy.[23] We did not assess the influence of other less important characteristics separately (eg, population size, age distribution and enrollment patterns, other-cause mortality, digital rectal examination, or biopsy sensitivity). However, we believe we have accounted for the characteristics most likely to be influential.

Using the cure parameter estimated for the ERSPC trial in the PLCO setting, we obtained a prostate cancer mortality reduction of 6% to 8%. This indicates that if PSA testing in the PLCO trial had been as efficacious as in the ERSPC trial, the circumstances of its implementation (eg, infrequent receipt of biopsies, high contamination, healthy screenee effect) would likely have resulted in a modest reduction in prostate cancer mortality. This result is consistent with our prior study, in which we demonstrated that contamination increased the mortality rate ratio and decreased the power of the trial to detect a mortality difference from 40% to 70% to 9% to 25%.[19]

Initially, we planned to consider a symmetric approach, by also starting from the PLCO cure parameter and working toward more ideal situations, and back to the ERSPC. However, the best-fit cure parameter for the PLCO was 0, and when there is no benefit, it is impossible to examine how the benefit depends on the circumstances of implementation. A limitation is that this result depends on how much of the lower than expected mortality is attributed to changes in baseline survival compared with the pre-PSA era (eg, due to improvements in care) rather than screening benefit in both arms. We believe our approach and prediction is valid in that one trial has shown an effect of the earlier treatment of screen-detected lesions, and that the other trial has been underpowered.

In assessing the efficacy of any screening test, it is important to recognize that results will depend on how the test is implemented. If we started with a cure parameter estimated for the ERSPC trial, then under idealized circumstances (no control arm contamination, perfect attendance, perfect compliance with biopsy recommendations [run 5]), the models predicted an approximately 40% mortality reduction after 11 years, which is greater than the 21% reduction observed. However, under real-world circumstances of control arm contamination and less than perfect attendance and biopsy compliance as in the PLCO trial, the models predicted a much lower mortality reduction, on the order of 6% to 8%. Thus, the trials are likely less inconsistent than their results suggest. Furthermore, the benefit of PSA screening under idealized circumstances is likely more than the trial results suggest. It could be as high as 40%, which previously has been reported to suggest a net benefit and a reasonably favorable tradeoff when accounting for the main harms of PSA screening.[16,32] However, specialized methods will be required to extract an estimate of what this idealized benefit might be based on the data from both trials.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

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