Mortality reductions produced by sustained prostate cancer screening have been underestimated

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Abstract

Background/Rationale: PSA-based screening in the recently reported European Randomized Study of Screening for Prostate Cancer (ERSPC) was reported to have reduced the rate of death from prostate cancer by a mere 20%. However, this number is an underestimate, caused by (i) including in the 20% the years before the impact of the first screen become manifest, and (ii) not having full information for the follow-up years where the effects of the screening are most apparent. The first of these sources of error can be avoided by using time-specific measures. This article reports the results of a re-analysis of the results of this trial using this form of analysis.

Methods: Mortality rate ratios for each of follow-up years 1-12 were derived from the yearly numbers of prostate cancer deaths and numbers of men being followed in each arm of the ERSPC. To reduce statistical noise, they were based on moving 3-year intervals. In addition, to further reduce the statistical noise, a smooth rate ratio curve was fitted to the yearly data in order to measure the steady state reduction in mortality, and to identify the time at which it reached this level.

Results: A re-analysis of the prostate cancer deaths in the first 12 years of follow-up in the ERSPC suggests that the sustained reduction in prostate cancer mortality may be as much as 50%. A more precise estimate cannot be made until the critical data from 2007 and 2008 -- and beyond -- are included in the analysis.

Discussion: Re-analysis of the ERSPC data suggests that if screening is carried out for several years, and if follow-up is pursued until the reduction becomes manifest, the reduction in mortality will be 50-60%. An analysis that includes the 2007-2008 follow-up data is required to quantify more precisely the impact of this intervention.

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INTRODUCTION

The European Randomized Study of Screening for Prostate Cancer (ERSPC), which began enrollment 19 years ago, accrued 162,000 men. The ERSPC publication, in March 2009\(^1\), reported a reduction in prostate cancer mortality due to screening of 20%. This disappointing result has prompted a number of organizations and authorities to rethink their prostate cancer screening efforts and their public health messages.

However, as is shown below, the 20% reduction is a substantial underestimate, for two reasons. First, there is a substantial delay between the time screening starts and the time the effect is expected to be observed; the estimated 20% is an average of the null reductions in years 1-7, before benefits could became apparent, and the substantial reductions that began to appear from year 8 onwards. Second, the (proportional-hazards-type) summary measure (the 20%) is sensitive to the duration of follow-up, which closed at the end of 2006, after an average of just 9 years of follow-up (range 3-15). A re-analysis of these ERSPC data that uses yearly rate ratios to avoid these two sources of error suggests a mortality reduction, due to screening, of more than 50%. However, a more precise measure will not be available until the critical data from 2007 and 2008 -- and beyond -- are included in the analysis.

METHODS AND RATIONALE

Five randomized trials of prostate cancer screening have now been reported. The numbers of men invited to the screening arm in the two Swedish studies\(^2\)\(^3\) were 1,500 and 2,400 respectively. The Quebec\(^4\) and U.S.A.\(^5\) studies enrolled a combined total of 123,000 men (69,000 in the combined screening arms), but in each of these two studies, the actual screening activities in the screening and control arms differed so little that at best only a small difference in
prostate cancer mortality could be expected. The ERSPC enrolled 162,000 men aged 55 to 69 at intake. The larger sample size and substantial difference in the participation rates in the two arms meant that it has considerably greater resolving power.

In the ERSPC report, the effect of screening on prostate cancer mortality was expressed as one number, derived from the numbers of prostate cancer deaths over the entire period of observation available for each man (range 3-15, average 9 years). Over this period, there were 214 prostate cancer deaths in 643,401 man-years of observation in the screening group and 326 in 785,585 man-years in the control group. These are the basis for the reported rate ratio of 0.80, and the conclusion that “PSA-based screening reduced the rate of death from prostate cancer by 20%” [95% CI: 2% to 35%]. Figure 2 of the NEJM article also contained a graph showing, for each arm, the “cumulative risk” of death from prostate cancer. The two curves in this key graph are redrawn in the current Figure 1A. On the basis of these curves, the authors did note that “the rates of (prostate cancer) death in the two study groups began to diverge after 7 to 8 years and continued to diverge further over time”. Unlike the authors, I now quantify this divergence, since it provides a more appropriate and meaningful measure of the reduction in mortality produced by screening than the reported 20% figure.

When studying the results of interventions which have virtually immediate effects, such as vaccinations\(^6\), many medications\(^7\), and screening for abdominal aortic aneurysms\(^8\), it is logical to cumulate the outcome events from the time the intervention commenced, and to report a single rate ratio derived from a proportional hazards model. However, as is seen in Figure 1A, there is a delay of several years until the benefit of prostate cancer screening becomes manifest and a single average mortality reduction, obtained by cumulating all prostate cancer deaths, will underestimate the effect\(^9\)\(^10\)\(^11\). This underestimation is considerable if the period of follow-up
before the intervention has any effect makes up a substantial portion of the entire period of follow-up available. Underestimation will also result if the follow-up does not extend far enough to include the period when the effects of sustained screening become most apparent. Both the timing and extent of the reduction become much more evident if one examines prostate cancer mortality in intervals of the follow-up (one-year intervals will be used here).

Therefore, I derived year-by-year mortality rate ratios from the yearly numbers of prostate cancer deaths and numbers of men being followed in each arm. To do so, I first saved the pdf file containing Figure 2 of the NEJM report into an encapsulated postscript (eps) file format; from this eps file, I then extracted the exact information (namely, the co-ordinates of the line segments and dots) that the statistical program, Stata, had used to draw the two Nelson-Aalen cumulative hazard curves. The eps file contained the exact co-ordinates of each of 89,308 and 72,837 line segments or dots, one per man. The horizontal and vertical co-ordinates of each of these segments/dots provided me with the exact numbers of men being followed at each point in follow-up time, and thus at the exact times of the vertical steps in the curves (corresponding to prostate cancer deaths). The number of prostate cancer deaths at each time point was obtained by multiplying the size of the step by the number being followed at that time. The numbers were then aggregated by year and study arm to produce the counts listed in Figure 1B.

Given the paucity of follow-up beyond year 12, I limited the re-analysis to the yearly mortality ratios for each of the first 12 years. To reduce the statistical noise, I based them on the deaths in moving 3-year intervals, so that the ratio and upper limit of the 95% CI shown above a given year is based on the data for that year together with those in the years immediately preceding and following it; those for year 12 are based on the numbers of deaths in years 11 and 12 combined. The total number of prostate cancer deaths in year one was fewer than 10, and so a
The rate ratio for this first year is not shown.

Despite this strategy to reduce noise, the observed prostate cancer mortality rate ratios in the ERSPC did not follow a perfectly smooth time-curve. This is understandable, as each of the two numerators that contribute to each observed rate ratio is subject to separate Poisson variation that is substantial when event rates are low; the observed fluctuations may also reflect the merging of data from seven ERSPC countries with somewhat differing screening intensities and differing durations of follow-up. Thus, in order to measure the steady state reduction in mortality, and to identify when it reached this level, as precisely as the data allow, a formal statistical procedure was used to fit a smooth rate ratio function to the mortality data, grouped into bins 1/5 of a year wide. I used as candidate curves those with the same general form as the one fitted in Figure 1B, since repeated four-year screening interval was used in the countries that contributed more than 80% of the men, and the death rate in the screening arm would not be expected to have begun to revert upwards towards that in the control arm until after the end of year 12. The curve has three parameters, when the mortality rate ratio first declines, the steady state reduction that is reached, and when it is reached. The when (i.e. the length of the delay until the reduction reaches a steady state) is a function of the screening regimen, and cannot be specified in advance, although it is expected to be several years. Thus I derive it from the observed data, using the method described in the Supplementary Material. The use of a formal curve-fitting approach to provide the best-fitting values of the curve’s three parameters removes the element of subjectivity: otherwise, different readers might “see” different degrees of reduction in the same set of rate ratios shown in Figure 1B.
RESULTS

The yearly numbers of prostate cancer deaths in each ERSPC arm, along with the mortality rate ratios for the intervals centered on years 2 to 12, are shown in Figure 1B. They indicate that after an expected delay (which the data indicate is approximately 7 years), the prostate mortality reductions that become evident in years 9 and beyond are statistically significant and considerably greater than the reported 20% reduction in the rate of prostate cancer deaths.

A formal curve fitting was also performed. Not surprisingly, the best (Maximum Likelihood) estimate is that, although the rate ratio became non-null starting at approximately 6.5 years, the steady state reduction has not yet been reached: the point estimate so far is a sustained 67% reduction (80%CI 30% to 89%) beginning at year 12. Moreover, as can be seen from the wide confidence region, the numbers of deaths are not sufficient to establish its timing and magnitude more precisely.

DISCUSSION

The ‘downsides’ of PSA-based prostate cancer screening have been well documented and long since been agreed upon. In order to document the ‘upside,’ five randomized trials -- the first of these begun 23 years ago -- involving a total of 321,000 men in 10 countries, and with an average follow-up ranging from 7-15 years, have sought to measure the reductions in prostate cancer mortality achievable by this screening. The first Swedish study use a 1:5 randomization to enroll 1,500 men in the screening arm; the first two rounds of screening, in 1987 and 1990, involved DRE only, while those in 1993 and 1996 added PSA. While 78% of the screening invitees underwent some screening, half of the men with screen-detected tumours did not receive
any treatment after diagnosis. Some 1.3% of those invited, and 1.3% of those not invited, had
died of prostate cancer by March 2003. In light of these features of the trial, the risk ratio of 1.0,
and the associated 95% CI of 0.6 to 1.6, are nor surprising. In the other Swedish study, which
used a 1: 10 randomization, 2,400 men were invited to one round of screening involving DRE
and PSA. Some 74% invitees accepted; only 11 of the 41 men offered treatment with curative
intent for their screen-detected cancers underwent radical prostatectomy, while “the remainder
were offered treatments which today are considered obsolete.”3 Thus, the prostate cancer
mortality ratio of 1.1, and associated 95% CI of 0.8 to 1.5, were, again, to be expected. The
screening in the Quebec and U.S. studies, begun in 1988 and 1993 respectively, involved PSA
from the outset, and involved more sizeable numbers of men (47,000 randomized 2:1, and
77,000 randomized 1:1, respectively), and repeated PSA-based screening. However, there were
only limited differences in the actual screening activity in the contrasted arms in each trial. Only
24% of the invitees in the Quebec trial were screened. Whereas the rates of compliance in the
screening group in the U.S.A. trial were 85% for PSA testing and 86% for digital rectal
examination, the rates of screening in the control group were also very high, increasing from
40% in the first year to 52% in the sixth year for PSA testing and ranging from 41 to 46% for
digital rectal examination. Moreover, the results of the U.S.A. study are largely driven by
prostate cancer deaths in years 1-7. In light of these features, and in light of the timing of the
reductions one would expect in a trial with a larger contrast in screening activity and sufficient
follow-up, the absence of a mortality reduction in the Quebec and U.S.A. trials is also not
surprising. The much larger ERSPC, with its much larger difference in screening activity in the
two arms, had considerably greater resolving power. Even though this resolving power has not
yet been fully utilized to measure the signal in the very follow-up time-window where it is
probably strongest, this potential can be achieved merely by collecting additional data.

Thus, the casual reader of the ERSPC report should not conclude that the best we can expect from PSA screening is a reduction in prostate cancer mortality of 20%. The time-specific re-analysis of the prostate cancer deaths in the first 12 years of follow-up suggests that if screening is carried out for several years, and if the follow-up is pursued into the window where the reduction in mortality becomes manifest, the reduction to be seen there will be 50-60%. However, although the ERSPC report was published in March 2009, the follow-up ended in December 2006, just when the pattern had begun to emerge. Thus, with the limited observations in the window where the screening benefits are expressed, it is not possible to put precise statistical bounds on this reduction, and so the prostate cancer deaths from 2007 onwards are crucial to more precisely measure the reduction achieved.

The re-analysis using yearly rate ratios avoided the dilution caused by averaging 7 years of (expected) non-reductions with 5 years of increasingly greater reductions, but it was not able to avoid the dilution and imprecision caused by inadequate follow-up. We await an analysis that includes this missing follow-up and that employs a time-specific approach.

Whatever the full mortality reductions turn out to be, those who might wish to “purchase” them need to know how much they cost. Some¹² may well consider that even if screening could achieve a sustained reduction of 67%, (or even 97%!) the very low prostate mortality rates in the control group means that the small absolute reductions will be achieved at an unacceptable cost. (So far, only 326 or 0.36% of the 89,353 men in the control group have died of prostate cancer; our theoretical calculations suggest the number will approximately triple by follow-up year 20.) However, all would agree that biases in the estimation of benefit need to be avoided. Moreover,
in view of the effort and resources that have been expended on the ERSPC thus far, it is worth pursuing a much more precise measure of the mortality reduction than the data in the 2009 report were able to provide.

The present re-analysis follows the intention to treat principle, using time-specific rates to reveal the non-proportional hazards pattern expected with screening data. The objective curve-fitting approach used in Figure 1B avoids the need to “pre-specify” when the reduction reaches steady state; it does specify the smooth form of the rate-ratio curve, but allows the data themselves to inform us about the two essential parameters that determine it, namely the timing and extent of the prostate cancer mortality reduction caused by screening.

A time-specific analysis is, of course, only necessary when the effect of the intervention is delayed, as in the case of prostate cancer screening. By contrast, screening for abdominal aneurysms produces an immediate and sustained reduction in mortality from ruptured aneurysms, and the cumulative mortality, in this case, fully captures the benefit of screening. The results of a program of screening competitive athletes for potentially lethal cardiovascular abnormalities\(^{13}\) is a further striking example of the shape of the ‘response function’ with time, and the role of screening intensity in this. Recognition of the difference between interventions with immediate and delayed effects should prompt similar re-analyses of the data from trials of screening in other cancers, and similar analyses in yet-to-be reported cancer screening trials.

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**Conflict of Interest:** None.  

**Ethics Committee Approval:** Not applicable.
Legend for Figure 1

Comparison of prostate cancer mortality rates in two arms of European Randomized Study of Screening for Prostate Cancer (ERSPC).

The graphs and numbers in this figure are based on the individual-patient-data extracted from the individual-level postscript commands used to Figure 2 of the NEJM report. For details on how these individual data were extracted, see the Methods section of the present report.

(A) Cumulative mortality curves, presented in the same format as in the original publication. As noted by the authors, “the rates of (prostate cancer) death in the two study groups began to diverge after 7 to 8 years and continued to diverge further over time”. However, they included the years of zero effect in their estimate of a reduction of overall average mortality of 20% (mortality rate ratio 0.80). *This is not an appropriate measure of the impact of screening, since the numbers of cures attributable to the screening in year 1 to year T only become apparent (as lower mortality rates in the screened than the control arm) in year (1 + ?) to year (T + ??)*. Note that T varied somewhat across the 7 ERSPC countries, and is used in a generic sense here.

(B) Yearly prostate cancer mortality rate ratios, used for re-analysis. These are designed to measure the timing and extent of the prostate cancer mortality reduction in years (1+?) to (T+??) as a result of the screening in years 1 to T. Each rate ratio was calculated by dividing the observed rate of prostate cancer deaths in the screening arm by the corresponding rate in the control arm. The rate ratio shown above a given year is based on the data for that year together with the data in the years immediately preceding and following it. The upper end of each vertical line denotes the upper 95% limit of the percentage reduction in prostate-cancer mortality: the reductions in the 3-year intervals centered on years 9 and beyond are statistically significant. The dotted line, with an asymptote of 64%, beginning at 12 years, was fitted using the method of Maximum Likelihood (see Appendix 1). The two shaded regions represent the 50% and 80% confidence regions for these two parameters. The 80% CI associated with the 67% asymptote, derived from the vertical range of the lighter grey region at 12 years, is 30% to 89%. The yearly numbers of prostate cancer deaths and of men being followed, shown at the bottom of the graph, as well as the rate ratios, are derived from the individual-patient-data extracted from Figure 2 of the NEJM report.

The results of the re-analysis using time-specific rate ratios indicate that the cures attributable to the screening in study year t only begin to become statistically apparent by year t+7 and later. They also indicate that of those in the control arm who died (or will die) of prostate cancer in years 8-12 of the study, possibly as many as half of them would not have died of prostate cancer had they been offered the program. The 25% - 60% reductions seen in years 8-12 of the study suggest a much greater numbers of cures attributable to the screening in year 1 to year T than the single overall 20% figure reported in the original article, but further follow-up data are required to make a precise estimate.
References


Prostate Cancer Mortality Rate Ratio

\[
\frac{S}{C}
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Follow-Up Year:

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Cumulative Prostate Cancer Mortality By End of Follow-Up Year:

Control Arm (C)  Screening Arm (S)

Percentage Reduction in Year-Specific Prostate Cancer Mortality Rate

\[(C - S) \text{ as } \% \text{ of } C\]
Supplementary Material for

Mortality reductions produced by sustained prostate cancer screening have been underestimated

1. The need for time-specificity in the analysis of data from cancer screening studies

Figure 1A and Supplementary Figure A show when it is and is not possible to use ratios of overall (or cumulative) cancer mortality rates to measure the timing and magnitude of the reductions produced by screening. Figure 1B includes a smooth-in-time rate ratio curve that was fitted to the ERSPC data. This appendix contains a more extensive discussion of the need for time-specificity, and provides details on how the smooth curve was fitted.

Since the first cancer screening trials, investigators have tried to avoid the dilution caused by including cancer deaths that occur after the window in which the benefits of the regimen become manifest. The recognition that the dilution caused by including those that occur before this window is more recent, and the message to avoid it has gone largely unheeded.

This ongoing time-insensitivity in the analysis of screening trials is all the more surprising today, where reviewers routinely ask whether the data justify the use of a proportional hazards model, i.e., of a single (average) hazard ratio. But even if we did not yet have screening data, biological principles alone suggest that this ‘constant-over-time right-from-the-outset reduction’ assumption may govern the time-pattern of the effects of screening for some conditions, such as abdominal aortic aneurysms, but not for cancers.

What has not been previously recognized is the considerable influence of the duration of follow-up, particularly in prostate cancer where the time scale is longer than for other cancers. Baker termed the dilution caused by including excessive/superfluous years in the time window...
after the effect of the last screen become manifest “post-screening noise.” In contrast, in trials of sustained prostate cancer screening, such as ERSPC, the attenuation is caused by (i) including the years before the impact of the first screen become manifest, and (ii) not having full follow-up information available on the years where the effects of the screening are most apparent.

These distortions argue for a data-analysis approach that cannot be influenced by, and is insensitive to, the choice of the time horizon of interest, the time window in which the effect of the screening regimen becomes manifest, and the amount of follow-up at the time of data-analysis. The measure should be robust to these and be calculable objectively from the data.

In Figure 1B, we subject the ERSPC data to formal quantitative time-specific analysis. Each time-specific rate ratio is independent of the ratio calculated from any another portion of the follow-up. The curve shows the timing of the delay until the effect of the screening regimen is expressed.

2. Fitting a smooth-in-time mortality rate ratio function.

In screening trials, the yearly observed numbers of cancer-specific deaths from the target cancer in each study arm are small, and so yearly mortality rate ratios fluctuate widely. For example, if the expected number in the non-screening arm for a particular year is 25, the actual count could vary by more than two-fold: under the Poisson law, it could range from about 15 to 35. Similarly, if the expected number in the screening arm was 16 (a true reduction of 36%), the actual count could vary from maybe 8 to 24, so that the observed rate ratio could vary from 0.3 (70% reduction) to 1.2 (20% increase). With event rates of this order of magnitude, it is difficult even with sample sizes in the tens of thousands to objectively estimate the true timing and extent of
the benefit of the intervention “by eye”. Thus, a formal curve-fitting procedure becomes important to smooth out the noise.

In this section, we describe – and show how to fit -- the simplest candidate curve for the rate ratios characterizing the results of a cancer screening program comprising several rounds of screening. The assumed form of the rate ratio curve (the fitted version is shown as a dotted line in Figure 1B) is such that it has a value of unity for some unknown number of years, begins to descend after this unknown time point, and descends to an ‘asymptote’ of unknown value some unknown number of years later, and remains at this value thereafter. If this simplest of all models is postulated, there are only three unknowns to be estimated, when the rate ratio began to be non-null, the value of the RR asymptote and the time at which the asymptote began. More complex curves, such as would be needed to smooth curves that show transient reductions, can be fitted in the same way, simply by changing the form of $RR(t)$ and adding more parameters. To do so, one would, naturally, require more extensive and more detailed data.

Consider a theoretical rate ratio (RR) curve, of the same shape as the one depicted by a dotted line in Figure 1B. Suppose the RR begins to change (become non-null) at $T_c$, and that its asymptote has the value $RR_a$, beginning at time $t = T_{\text{begin}}$.

Let it be defined as

$$RR(t) = \begin{cases} 1 & \text{until } t = T_c \\ 1-\{0.1, 0.2, 0.5, 0.8, 0.9\} \times (1 - RR_a) & \text{from } t = T_c \text{ to } T_{\text{begin}} \text{ [5 equal } t \text{ steps]} \\ RR_a & \text{from } t = T_{\text{begin}} \text{ onwards} \end{cases}$$

Suppose the data consist of:

- the times, $t_1, t_2, \ldots, t_D$, measured from randomization to screening/not, of each of the $D$ prostate cancer deaths in the two arms combined.
- the corresponding indicators, $s_1, s_2, \ldots, s_D$, of whether they occurred to men in the screening arm (1) or control arm (0).
the corresponding denominator-ratios, $dr_1$, $dr_2$, …, $dr_D$, where $dr_i$ is the ratio of the numbers of men being followed in the screening and comparison arms at the time of the $i$-th prostate cancer death.

The values of the three parameters, $T_c$, $RR_a$ and $T_{begin}$ can be estimated by numerically maximizing the Likelihood constructed by treating $s_1$, $s_2$, …, $s_D$ as realizations of $D$ Bernoulli random variables, where the expected value of the $i$-th such random variable is $dr_i \times RR(t_i)/[1 + dr_i \times RR(t_i)]^7$. The profile log likelihood can be used to obtain a C% confidence region for the $RR_a$ and $T_{begin}$ parameters by searching for those other pairs of these two parameter values that produce $2 \times \text{ProfileLogLikelihood}$ values that differ by less than a given amount from the value of the $2 \times \text{ProfileLogLikelihood}$ evaluated at the MLE (this amount is the $C^{th}$ percentile of the Chi-square distribution with 2 df).

The $t$’s, $s$’s and $dr$’s may not be available at the level of the individual, but the numbers of deaths $S$ and $NS$ in the screening and non-screening arms within each say one or half-year interval of follow-up may be known, along with the value of each “denominator ratio” $DR$, i.e., the ratio of the person-years lived in the interval by those in the screening and comparison arms. With such data, we can use the same conditioning as above, and regard the value of $S$ for interval centered on $t_{mid}$, conditional on the total number $S + NS$, of prostate cancer deaths in the interval, as the realization of a binomial random variable with expectation $DR \times RR(t_{mid})/[1 + DR \times RR(t_{mid})]$.

The second derivative of the profile Log-Likelihood can be used, along with cancer-specific and all-cause mortality rates, to calculate in advance what precision/power will be achieved with various numbers of subjects and durations of follow-up.

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Supplementary Figure A

Timing of effects of screening in disease processes with different natural histories: cumulative cause-specific mortality as reported in the Multicentre Aneurysm Screening Study (MASS) and the European Randomized Study of Screening for Prostate Cancer (ERSPC). The MASS enrolled 68,000 men aged 65-74 and involved a one-time screen with immediate treatment or surveillance of detected abdominal aortic aneurysms. As noted by the authors, “The benefit seen in earlier years of follow-up was maintained in the later years of follow-up, with continued divergence of the cumulative curves of deaths related to abdominal aortic aneurysm in the two groups”. The overall mortality rate reduction of 48% (mortality rate ratio 0.52) is an adequate and accurate measure of the impact of screening. The ERSPC enrolled 162,000 men aged 55-69 and involved repeated PSA-based screens 4 years apart. As noted by the authors, “The rates of (prostate cancer) death in the two study groups began to diverge after 7 to 8 years and continued to diverge further over time”. The overall mortality rate reduction of 20% (mortality rate ratio 0.80) is an inadequate and inaccurate measure of the impact of screening.
References


Timing of Screening Effects (as seen in cumulative cause-specific mortality curves)

Abdominal Aortic Aneurysms (One-off Screening, MASS)

Prostate Cancer (q 4y, ERSPC)

Control Arm
Screening Arm

Cumulative Cause-Specific Mortality