

Concerns With “New Evidence for the Benefits of Prostate-specific Antigen Screening: Data from 400,887 Kaiser Permanente Patients”



TO THE EDITOR:

I read with interest the recent retrospective cohort review of prostate-specific antigen (PSA) screening, and was impressed with the effort to quantify screening benefits.¹ This was an innovative means of studying this important topic. However, 3 study assumptions create errors that call the conclusions into doubt.

(1) Population grouping introduces bias

Dr. Alpert stratified the population by PSA screening interval. Since PSA screening was standard of care, patients with less screening likely received less health care overall. Groups with less screening were likely biased in race, socioeconomic status, and other risk factors that affect prostate cancer mortality. No patient demographics were included in the report or the supplement.

The difference in prostate cancer detection rates between groups demonstrates these health disparities. The No Prior Screening group had quadruple the prostate cancer diagnoses as the regular screening (12-18 months) group. Cancer detection should be significantly higher with regular screening since PSA screening has over diagnosis rates of 16%-40%.² The higher prostate cancer rate without prior screening must reflect population differences.

(2) Exclusion criteria reduce cancer in screened groups

The study exclusion criteria add additional bias by creating populations with different prostate cancer prevalence. Patients with diagnosed prostate cancer were excluded. Because PSA screening was standard of care, patients with regular screening during the study interval likely received regular screening prior to 1998, while those in the No Prior Screening group likely received less regular screening. The regularly screened group would have more prostate cancers patients diagnosed and eliminated. Since the regularly screened population was more often verified cancer-free, why would we not expect higher survival? A number needed to screen or diagnose cannot be calculated since the statistics assume similar prostate cancer prevalence.

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(3) All-cause mortality estimate not rigorous

The 24% decrease in all-cause mortality with screening was the most dramatic finding. Overall survival was estimated by calculations to account for risk differences. Since the No Prior Screening group had higher overall mortality, Dr. Alpert calculated the nonprostate cancer mortality of the regularly screened group by subtracting prostate cancer mortality from total mortality. He then adjusted the No Prior Screening group to have identical nonprostate cancer mortality.

There are 2 major concerns with this method. By equalizing mortality not relating to prostate cancer, the author only showed that higher prostate cancer mortality translates to higher all-cause mortality. With less prostate cancer in the regular screening group, the conclusion becomes one of higher prostate cancer mortality in a population with more prostate cancer. This estimate also adds significant uncertainty because errors inherent in each statistic are combined in each of the 2 calculations. These calculations were not evaluated with confidence intervals or other statistical analysis.

Given these concerns, the conclusions cannot be accepted as presented. Perhaps, Dr. Alpert can correct his analysis for other health markers between groups. Until then, the only substantiated conclusion is that less healthy men are more likely to die of both prostate cancer and other causes.

References

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Reply by Author: “New Evidence for the Benefits of Prostate-Specific Antigen Screening”



TO THE EDITOR:

Before detailing my responses, I want to say that in the commentator's reading of my data tables there seem to be

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some misinterpretations, and in his estimate of the potential impact of the noted problems, the likely effect is greatly exaggerated. In addition, he fails to look at the concordance between this study and others using similar parameters and testing intervals – the cumulative across study analysis that is as important in a scientific approach as the hunt for potentially problematic imperfections.

Population grouping introduces bias. While the commentator is correct that the unscreened group is less healthy than the 12-18 months screened group and has a higher incidence of cancers, the increased incidence of cancers is nowhere near the quadruple increase claimed. For subjects aged 55-74, there was a 25% higher cancer incidence among the unscreened. To correct for this difference and make the incidence of cancer equal in the 2 groups, we can subtract 530 cancers, and 65 cancer deaths from the No Prior group. Although the calculation now shows a 53% relative risk reduction in prostate cancer deaths (95% confidence interval [CI] 36%-69%, $P < .001$), rather than the reported 64%, this is still an enormous benefit.

Exclusion criteria reduce cancer in screened group. While the commentator is correct, the likely effect is again exaggerated. The benefit of screening drops off rapidly after 12 months. Consequently, this objection applies in a substantial way only to the 1998 subjects and becomes increasingly insignificant for subjects in subsequent years. In addition, the correction above already compensates for this small disparity.

All-cause mortality estimate. While the commentator is not correct about my not having provided statistical confidence measures, I agree that the data for these calculations were affected as described above. However, using the same correction method as above, the reduction in all-cause deaths at 12-16 years of follow-up goes from 24% to 16% (95% CI 11%-21%, $P = .001$), which is still an enormous benefit.

External validation of this study. The Kaiser PSA study shows that the 12-month screening interval is highly effective, with benefits falling off dramatically with longer intervals. These results are fully compatible with the randomized controlled trials, with differences in screening intervals accounting for the marked disparity

between studies. Since our findings indicate no benefit to screening at intervals of 4 years or more, it is consistent with these findings that the studies showing no effect of screening (Finnish subset of the ERSPC,¹ CAP Trial,² and Stockholm study³) all used screening intervals that were uselessly long. In contrast, the 1988 Quebec trial⁴ using yearly screenings, found a 62% decrease in cancer mortality – a number remarkably similar to the Kaiser study. Similarly, in the Göteborg subset of the ERSPC study⁵ which used a 2-year screening interval, the data showed a 44% reduction in prostate cancer deaths, a number very close to the 2-year interval data from the Kaiser study.

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