

10.3.A Prostate Cancer Screening

Andriole et al [1] reported the prostate cancer screening results of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. This randomized trial compared prostate cancer screening using a combination of prostate-specific antigen (PSA) testing and digital rectal examinations with usual care (which was whatever the physician usually did, possibly including PSA screening). The subjects were 76,693 men aged 55 – 74 years. After 7 years of follow-up the results of an intention to treat analysis were as follows:

Randomized To...	Diagnosis of Prostate CA		Death From Prostate CA		Death from Other Causes		Total
	N	%	N	%	N	%	
Annual Screening	2820	7.35%	50	0.13%	2544	6.63%	38343
Usual Care	2322	6.05%	44	0.12%	2596	6.77%	38350

There were significantly more patients diagnosed with prostate cancer in the group randomized to annual screening (116 vs. 95 per 10,000 person-years, risk ratio 1.21; 95% CI: 1.15, 1.28). There were also more prostate cancer deaths in the group randomized to screening (2.0 vs. 1.7 per 10,000 person-years, risk ratio 1.14; 95% CI: 0.76, 1.70).

- a) What are 3 possible explanations for the greater reported death rate from prostate cancer in the screened group? Include at least 1 named bias.

- b) As mentioned above, the prostate cancer death rate was approximately 2.0 per 10,000 person-years. If a new intervention completely eliminated prostate cancer death, how many men would have to receive this intervention to prevent one death per year?

Back in 2011 the U. S. Preventive Health Services Task Force recommended against prostate cancer screening (a "D" grade)¹. This caused a big uproar. In an editorial in *USA Today* titled, "If PSA test saves lives, averages don't matter," the editors argued that it is better to know whether or not you have prostate cancer. Here's an excerpt from that editorial (available at: <http://www.usatoday.com/news/opinion/editorials/story/2011-10-10/PSA-test-prostate-cancer/50723714/1>)

The ...U.S. Preventive Services Task Force, doesn't dispute that the test detects cancer. Instead, it argues, with a formidable arsenal of data, that the test leads to widespread over-treatment, which outweighs the benefits of early detection. Over the entire society, it says, there is no net gain and substantial damage to patients, ranging from needless worry, to impotence and incontinence, to death.

And therein lies a dilemma for the older-than-50 male, for whom averages mean little. If he isn't tested, he'll be spared the false positives the test commonly produces as well as treatment risk. On the other hand, if he has high-grade cancer, the disease might not be found until it has spread to other organs, which is fatal. **The five-year survival rate for localized prostate cancer is 100%. Once the cancer reaches distant organs, the rate falls to 28.8%. [Emphasis added.]**

- c) For purposes of argument, assume that it takes prostate cancer exactly 7 years from the first spread to distant organs until it kills the patient and that it is equally likely to be detected any time during those 7 years.
- i) If treatment of prostate cancer has no effect on survival, what proportion of men whose prostate cancer is detected in distant organs will survive for 5 years or more?
 - ii) If treatment of prostate cancer has no effect on survival and death from prostate cancer occurs only after distant spread, what proportion of men whose prostate cancer is detected *before* it has spread to distant organs will survive 5 years or more?
 - iii) Even if treatment of prostate cancer has no effect on survival, could lead-time bias explain the 5-year rates quoted in the last 2 sentences of the USA Today editorial?
- d) Of course, the scenario in (c) is unrealistic; it was intended to rule out length-time (differing natural history) bias as a reason for shorter survival among men whose prostate cancer is detected after spread to distant organs. More realistically, some prostate cancers are more aggressive, spend less time in the localized in the prostate gland, and kill patients more quickly. Even if treatment of prostate cancer has no effect on survival, could length-time bias explain the 5-year rates quoted in the last 2 sentences of the USA Today editorial?

¹ In 2018 the USPSTF changed this to a C grade (offer or provide the service based on individual circumstances) for men aged 55 to 69. It's still a D grade (discouraged) for men 70 years old or older.

e) One concern, labeled "the elephant in the room" by Andrew Vickers,[2] is contamination (crossover): about 40% of patients in the Usual Care group had PSA testing the first year and this increased to 52% in year 6. Given the intention-to-treat analysis, what effect would this contamination have on the effect of being assigned to screening on each of the following outcomes?

- i. Prostate cancer incidence?
- ii. Prostate cancer mortality?
- iii. Total mortality?

References

1. Andriole GL, Grubb RL, 3rd, Buys SS, Chia D, Church TR, Fouad MN, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med.* 2009;360(13):1310-9.
2. Vickers AJ. Prostate Cancer Screening: Time to Question How to Optimize the Ratio of Benefits and Harms. *Ann Intern Med.* 2017;167(7):509-10.