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:

	Diagnosis of Prostate CA		Death From Prostate CA		Death from Other Causes		Total
Randomized To…	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.

1. **This increase could easily be due to chance; the 95% CI on the risk ratio extends well below 1.**
2. **Sticky diagnosis bias could lead to more deaths being labeled as due to prostate cancer; this possibility is supported by the slightly lower death rate from causes other than prostate cancer in the screened group.**
3. **Pseudodisease: maybe some of the deaths came from treating subjects with pseudodisease (e.g., post-operative deaths following prostatectomy for a cancer that never would have caused illness).**

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?

If the new intervention completely eliminated prostate cancer mortality, mortality in that group would be zero and the ARR would be 2 per 10,000 person years. So the NNT would be 10,000 person years/2 deaths = 5000 person-years/death. So 5000 men would need to be treated for one year to prevent one death. (Or if it was a treatment just delivered one time, like an operation or annual injection, 5000 men would need to be treated per year to prevent one death.)

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?

If prostate cancer is equally likely to be detected any time during the seven years between spread and death, then it will be detected in the first 2 years 2/7 of the time, and all of those patients and none of the rest will survive 5 years, so 5-year survival will be *2/7 = 28.6%*

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?

The problem stem says to assume it takes 7 years from first spread to death, so 100% will survive ≥ 5 years.

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?

Yes; lead time bias could explain the difference. Parts i and ii show that the numbers given are consistent with no effective treatment, even given a uniform natural history of prostate cancer (i.e., no length-time bias).

[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 (discourged) for men 70 years old or older.

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?

Yes. Cancer detected while still localized probably has a better prognosis anyway. An extreme of this would be pseudodisease. In fact, not all localized prostate cancer will eventually spread to distant organs. Some localized prostate cancer just sits around and never spreads. The patient ultimately dies of something else. Autopsy studies have shown this. Comparing survival between localized prostate cancer and metastatic prostate cancer is like comparing survival between patients with an upper respiratory tract infection and patients with pneumonia. An upper respiratory tract infection may sometimes progress to pneumonia, but that doesn't mean the comparison is fair.

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?

Th combination of contamination with an intention-to-treat analysis would diminish the apparent effect size for all outcomes. Mathematical modeling suggests PSA screening does have a small prostate cancer mortality benefit compared with no screening but also has significant harms, especially as currently implemented.[2]

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.