**Ch10.06.A. CT Screening for Lung Cancer**

The National Lung Screening Trial (NLST) randomized 53,454 current and former heavy smokers (minimum 30 pack-years) aged 55 to 74 years to either helical CT scanning or chest-x-rays annually for 3 years.(Aberle, Adams et al. 2011) There was a statistically significant (P=0.004) 20% relative risk reduction in the CT group. Results for lung cancer mortality and total mortality are summarized below.

| | Lung Cancer Mortality | | | |
|---|---|---|---|---|
| | Yes | No | Total | Risk |
| CT | 356 | 26,366 | 26,722 | 1.33% |
| X-Ray | 443 | 26,289 | 26,732 | 1.66% |
| Total | 799 | 52,655 | 53,454 | |
| | | | ARR= | 0.32% |

| | Total Mortality | | | |
|---|---|---|---|---|
| | Yes | No | Total | Risk |
| CT | 1,877 | 24,845 | 26,722 | 7.02% |
| X-Ray | 2,000 | 24,732 | 26,732 | 7.48% |
| Total | 3,877 | 49,577 | 53,454 | |
| | | | ARR= | 0.46% |

**a.)** State whether each of the following statements is true or false; explain your answer.

**i.** The favorable effect of annual CT screening on lung cancer mortality (compared with chest x-ray) can be explained by lead-time bias or length-time bias.

**False. This was a randomized trial, and when you compare mortality in the entire screened and unscreened groups, you can't have lead- or length-time bias. You have to compare survival among those with disease to get lead- or length-time bias.**

**ii.** Even though this is a randomized trial, a within-group comparison in the CT scan group would probably find longer survival in those whose cancer was detected by scanning (compared with those presenting with symptoms) at least partly due to length-time bias.

**True. Within-group comparisons don't have the benefits of the randomized trial design. Now you are comparing those diagnosed by symptoms to those diagnosed by screening – just the sort of comparison that is subject to length-time bias, because screening preferentially identifies slower growing tumors.**

**iii**. The apparent reduction in lung cancer mortality in the CT screened group could be due to "Sticky Diagnosis Bias."

**False. Sticky diagnosis bias is possible with comparisons of cause-specific mortality, but it would bias the results *against* screening because those in the screened group would be more likely to have their deaths attributed to lung cancer.**

**iv.** Because there was a trend towards decreased mortality due to causes other than lung cancer in the CT scan group, "slippery linkage bias" is unlikely to explain the apparent lung cancer mortality benefit.

***True. Slippery linkage bias leads to underestimation of the harms of screening. In order for slippery linkage bias to explain the lung cancer mortality benefit, deaths due to lung cancer in the screened group would somehow need to have been attributed to other causes. If this had occurred, then the non-lung cancer death rate would be higher in the screened group, but it's actually a little lower. The quick way to tell that this is the case is that the absolute risk reduction for total mortality is actually greater than the absolute risk reduction for lung-cancer mortality.***

**b)** The following is taken from the CBS News story about the study:
(http://www.cbsnews.com/stories/2010/11/04/eveningnews/main7023357.shtml)

> "After 50 years of smoking, 67-year-old Steffani Torrighelli knew she was at high risk for lung cancer. Two years ago she enrolled in [the] study, and sure enough a CT scan picked up an early stage tumor before she had any symptoms… Since Torrighelli's lung surgery two years ago, she's cancer free and vigilant about screening."
>
> Could Steffani's good outcome in this randomized trial be due to detection of pseudodisease? Explain.

***Yes. There is no way to know if her early stage lung cancer would have caused her any problems. Although some lung cancer deaths appear to have been prevented, we don't know how many unnecessary operations may have occurred to achieve that benefit. The mortality benefit in this randomized trial can't be due to pseudodisease, but good outcomes in individual patients can be.***

**c)** Assume that the lung cancer mortality benefit resulted from 3 years of annual CT scanning. About how many screening CT scans were needed to defer one lung cancer death in the NLST?

***The absolute risk reduction (ARR) was 0.0032. Therefore, the NNT = 1/ARR= 1/0.0032= ~300***
***1 scan/year × 3 years × 300 = ~900 screening scans.***

***A more precise answer could be obtained by dividing the 75,126 scans in the CT group (from Table 2 of the paper) by the number of deaths prevented, about 443-356=87 deaths (from the table above). This gives 75,126/87 = 863 scans to prevent one death.***

***An even more precise answer would take into account that the sample sizes in the CT and X-ray groups were not quite equal. So we could multiply the RRR of 0.199 by the death rate in the chest X-ray group to get the estimated death rate in the CT group, then multiply that by the N in the CT group to get an estimate of 88.6 deaths prevented. Dividing this into 75,126 gives 848 scans to prevent one death.***

**d)** Press reports say the scans cost about $300 each. What was the approximate cost of the screening CT scans per lung cancer death deferred?

The approximate cost would be ***$300 × 900 = $270,000. (The more exact answer using the 848 scans actually needed would be $254,400. Anything in this ballpark OK.)***

**e)** Counts of the invasive diagnostic procedures from Table 3 of the paper are excerpted below. Compared with annual chest x-rays, how many additional invasive diagnostic procedures (percutaneous cytologic examinations or biopsies, bronchoscopies and surgical procedures) were required per lung cancer death deferred?

| Excerpted from Table 3 | | |
|---|---|---|
| | CT | CXR |
| Total N | 26,722 | 26,732 |
| Percutaneous Cytologic Examinations or biopsies | 322 | 172 |
| Bronchoscopies | 671 | 225 |
| Surgical procedures | 713 | 239 |
| Total | 1706 | 636 |

***Answer: There were 1706 invasive procedures in the CT group, compared with 636 invasive procedures in the CXR group. Thus, there were roughly 1706-636 = 1070 extra procedures in the CT group to defer the ~88 deaths, or about 12.2 invasive procedures per lung cancer death deferred (compared with CXR screening). (This is only roughly correct because the sample sizes were not quite equal. So, a better estimate of excess procedures would be:***
***(1706 – 638)/26732 × 26722 = 1068.)***

Aberle, D. R., A. M. Adams, C. D. Berg, W. C. Black, J. D. Clapp, R. M. Fagerstrom, I. F. Gareen, C. Gatsonis, P. M. Marcus and J. D. Sicks (2011). "Reduced lung-cancer mortality with low-dose computed tomographic screening." N Engl J Med **365**(5): 395-409.