Ch.11.06. Axillary Node Dissection

Recall in Problem 1.4 we introduced axillary lymph node dissection (ALND) for breast cancer staging. An alternative to routine ALND is sentinel-node biopsy: removing one axillary lymph node to see if it has cancer in it and skipping the ALND if it does not. Investigators from Italy [1] compared these two strategies in 516 women with primary breast cancer tumors 2 cm or less in diameter. As expected, they found significantly less swelling, pain, scarring, and numbness or tingling in the women in the sentinel-node group. There also were fewer unfavorable events and deaths in that group, as shown in the table below:

	Axillary Dissection	**Sentinel-node Biopsy**
Number of subjects	257	259
Adverse events other than death (metastases, recurrences, etc.)	21	13
Deaths	6	2

The authors' conclusion was: "Sentinel-node biopsy is a safe and accurate method of screening the axillary nodes for metastasis in women with a small breast cancer."

An accompanying editorial, however, was critical of the Italian study because of its small sample size. [2] It cited two other trials in process as having adequate sample sizes, one with power to detect about a 2% (absolute) difference in survival and the other with power to detect a 5% difference. As the editorialists put it,

> "The era in which randomized clinical trials are dominated by a single institution — an approach that was perhaps justifiable in the past — is now over, since virtually no single institution can enroll enough patients to allow detection of small differences between two study groups...
>
> "The conclusion that sentinel-node surgery does not result in reduced survival and therefore that it is a safe procedure, equivalent to axillary dissection, must await the completion of larger clinical trials with sufficient power."

a) Subsequent trials [3, 4] have also found that routine ALND is unnecessary, but did we really need to wait until they were published? Assume that, as suggested by the editorialists, a < 2% absolute difference in total mortality would not be clinically significant. Output from Stata (csi command) to compare total mortality in the two groups is shown below. (The sentinel-node group is considered "exposed" and "cases" are deaths.)

```
. csi 2 6 257 251

                 |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
           Cases |         2           6  |          8
        Noncases |       257         251  |        508
-----------------+------------------------+------------
           Total |       259         257  |        516
                 |                        |
            Risk |   .007722    .0233463  |   .0155039
                 |                        |
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
 Risk difference |        -.0156243       |   -.0369425    .0056939
      Risk ratio |         .3307593       |    .0673847    1.623539
 Prev. frac. ex. |         .6692407       |   -.6235388    .9326153
 Prev. frac. pop |         .3359173       |
                 +-----------------------------------------------
                              chi2(1) =     2.06  Pr>chi2 = 0.1509
```

Based on the 95% CI, is a clinically significant (≥ 2%) increase in mortality with sentinel-node biopsy consistent with the findings?

The upper limit of the 95% CI for the risk difference is only a 0.5% increase in total mortality -- well below the 2% increase felt to be clinically significant by the editorialists. What seems to be an underpowered study may not be underpowered if the goal was to rule-out significant harm and the trend is towards benefit. (Similar conclusions apply to the adverse events other than death.)

b) Imagine that you had gone through your answer to part a with the editorialists, and they had remained skeptical. How would you explain their skepticism in Bayesian terms?

They might have had trouble believing the results because their estimate of the prior probability of lower mortality in the sentinel-node group was very low.

(They might also have felt scooped by the Italian study, since they were both authors of one of the trials in process at the time,[3] but that is not a Bayesian reason).

1. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med. 2003;349(6):546-53.
2. Krag D, Ashikaga T. The design of trials comparing sentinel-node surgery and axillary resection. N Engl J Med. 2003;349(6):603-5.
3. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927-33.

4. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017;318(10):918-26.