

10.4.A. Ovarian cancer screening

For the ovarian cancer portion of the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial, 78,216 women aged 55-74 years were recruited 1993-2001 at 10 US centers and randomized to be offered annual screening with transvaginal ultrasound and serum cancer antigen 125 (CA-125) vs. usual care. The initial mortality results for this trial were reported in 2011, [1] and 15-year follow-up in 2016.[2]

Figure 2 from the 2011 paper is reprinted below. The relative risk of being diagnosed with ovarian cancer was 1.21 (95% CI 0.99-1.48) and for ovarian cancer mortality the RR was 1.18 (95% CI 0.82, 1.71).

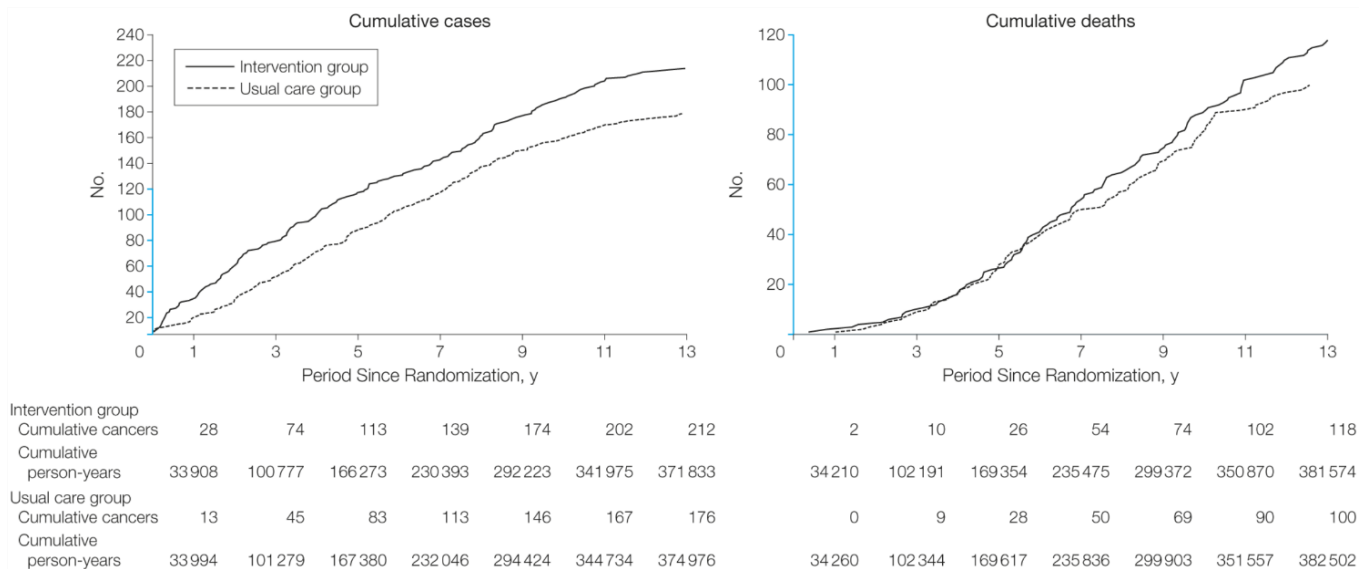


Figure 2. Ovarian Cancer Cumulative Cases and Deaths. Reproduced with permission from JAMA.2011.305(22):2295-2303. Copyright©(2011) American Medical Association. All rights reserved.

- a. Assume (as appears to be the case) that both cumulative cases curves level off over time and the usual care curve never catches the intervention curve. What is the most likely explanation (other than chance) for the excess of ovarian cancer diagnoses in the intervention group? Explain.
- b.) The difference in ovarian cancer mortality between the intervention and usual care groups could have been due to chance. Could a higher cause-specific mortality rate be explained by the following? For each possible option, say yes or no and explain your answer.
 - i) Sticky diagnosis bias
 - ii) Slippery linkage bias

iii) Overdiagnosis

iv) Length-time bias

c) Complications associated with diagnostic evaluation for cancer occurred in 45% of the women diagnosed with ovarian cancer in the screening group, compared with 52% of the women diagnosed with ovarian cancer in the usual care group. Do these point estimates suggest that screening was not associated with an excess of complications from diagnostic evaluations for ovarian cancer?

d. The report of the extended follow-up includes Figure 2b below, which compares ovarian cancer survival among those in the intervention arm whose ovarian cancer was diagnosed by screening with those whose cancer was diagnosed by other means. Survival was longer for screening detected cancers (log rank test $P=0.04$).

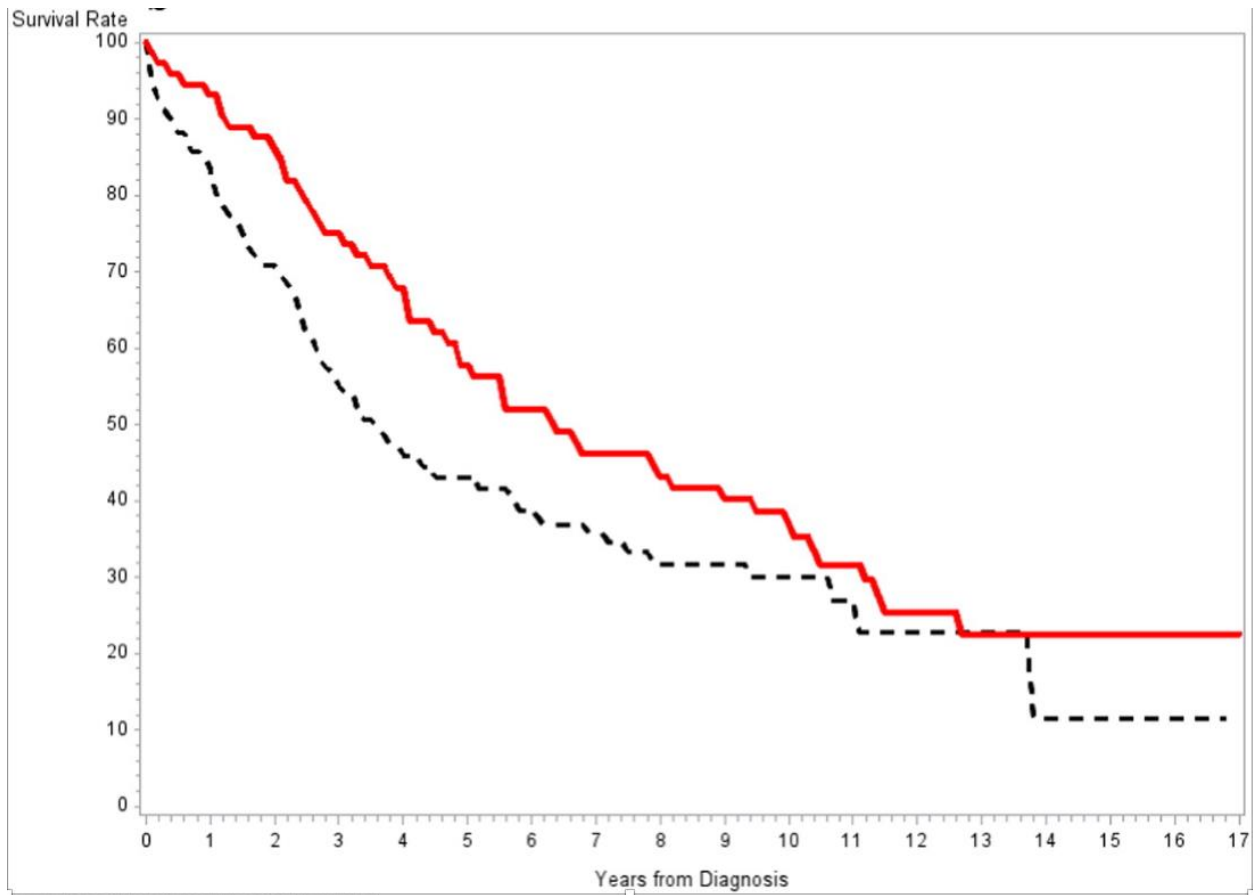


Fig. 2b) Ovarian cancer-specific survival by mode of detection in the intervention arm. Red (solid) line is for screen detected cases, black (dotted) line is for non-screen detected cases.

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- i.) With survival curves like Figure 2b sample size diminishes over time, so it's hard to tell whether differences after about 10 years are real. But let's suppose that after 12 years the survival curves actually come together and that leveling off of the red screen-detected cancer survival curve above the black dotted curve after 13 years is due to luck. If that were the case, would this figure be more consistent with overdiagnosis or lead time bias?

- ii.) Repeat the question above, but now assume that survival really does level off at a little over 20% in the screen detected group, but not in the other group. Now would the figure be more consistent with overdiagnosis or lead time bias?

REFERENCES

1. Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA*. 2011;305(22):2295-303.
2. Pinsky PF, Yu K, Kramer BS, Black A, Buys SS, Partridge E, et al. Extended mortality results for ovarian cancer screening in the PLCO trial with median 15years follow-up. *Gynecol Oncol*. 2016;143(2):270-5.