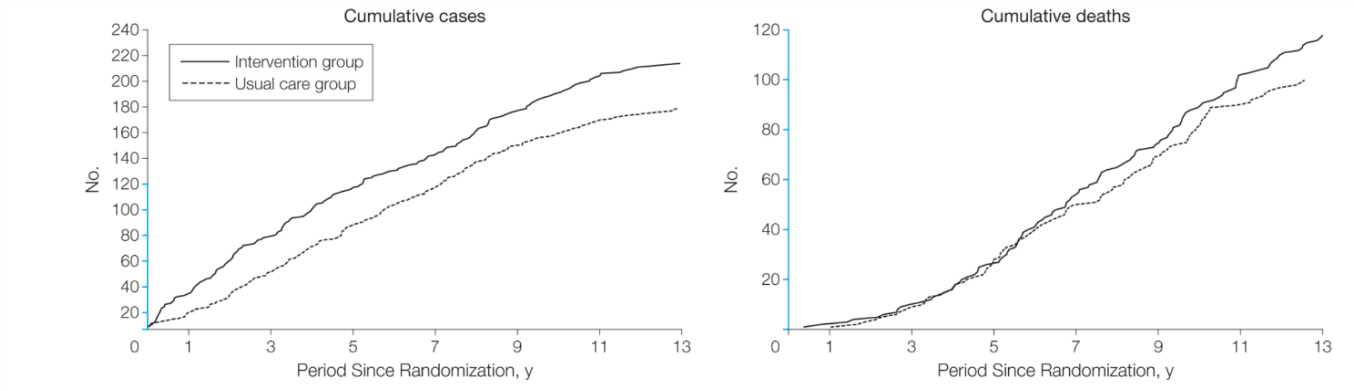
10.4.A. Ovarian cancer screening

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).



Intervention group							
Cumulative cancers	28	74	113	139	174	202	212
Cumulative person-years	33908	100777	166273	230393	292223	341975	371833
Usual care group							
Cumulative cancers	13	45	83	113	146	167	176
Cumulative person-years	33994	101279	167380	232046	294424	344734	374976

Intervention group							
Cumulative cancers	2	10	26	54	74	102	118
Cumulative person-years	34210	102191	169354	235475	299372	350870	381574
Usual care group							
Cumulative cancers	0	9	28	50	69	90	100
Cumulative person-years	34260	102344	169617	235836	299903	351557	382502

Figure 2. Ovarian Cancer Cumulative Cases and Deaths.

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.

Answer: The most likely explanation is pseudodisease. If all cancers diagnosed by screening eventually would have presented with symptoms, and they are just being caught sooner (lead time) we would expect the number of cancer diagnoses in the usual care group to catch up in later years of the study.

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

Yes. Sticky diagnosis bias can cause higher cause-specific mortality in the screening group.

ii) Slippery linkage bias

No. Should cause lower cause-specific mortality.

iii) Overdiagnosis

Yes, overdiagnosis could ***lead to harmful interventions that increase mortality.***

iv) Length-time bias

No. 1) Length-time bias doesn't occur when you compare the entire screened group to the entire unscreened group. 2) Even if it could occur, it would make screening look better.

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?

No, **these point estimates can't tell us whether screening was associated with an excess of complications from diagnostic evaluations for ovarian cancer.** ***It is not legitimate to count complications only in those diagnosed with ovarian cancer! Just as survival <u>in those diagnosed with disease</u> can be misleading (because the denominator can be inflated by overdiagnosis), the diagnostic complication rate can also be misleading if the denominator is either those ultimately diagnosed with the disease or those in whom the diagnostic evaluation was done. In an RCT like this one, diagnostic complications should be compared between the whole group randomized to screening vs. the whole group randomized to usual care. In fact, 95 women in the screened group had complications, compared with 91 assigned to usual care,***

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).

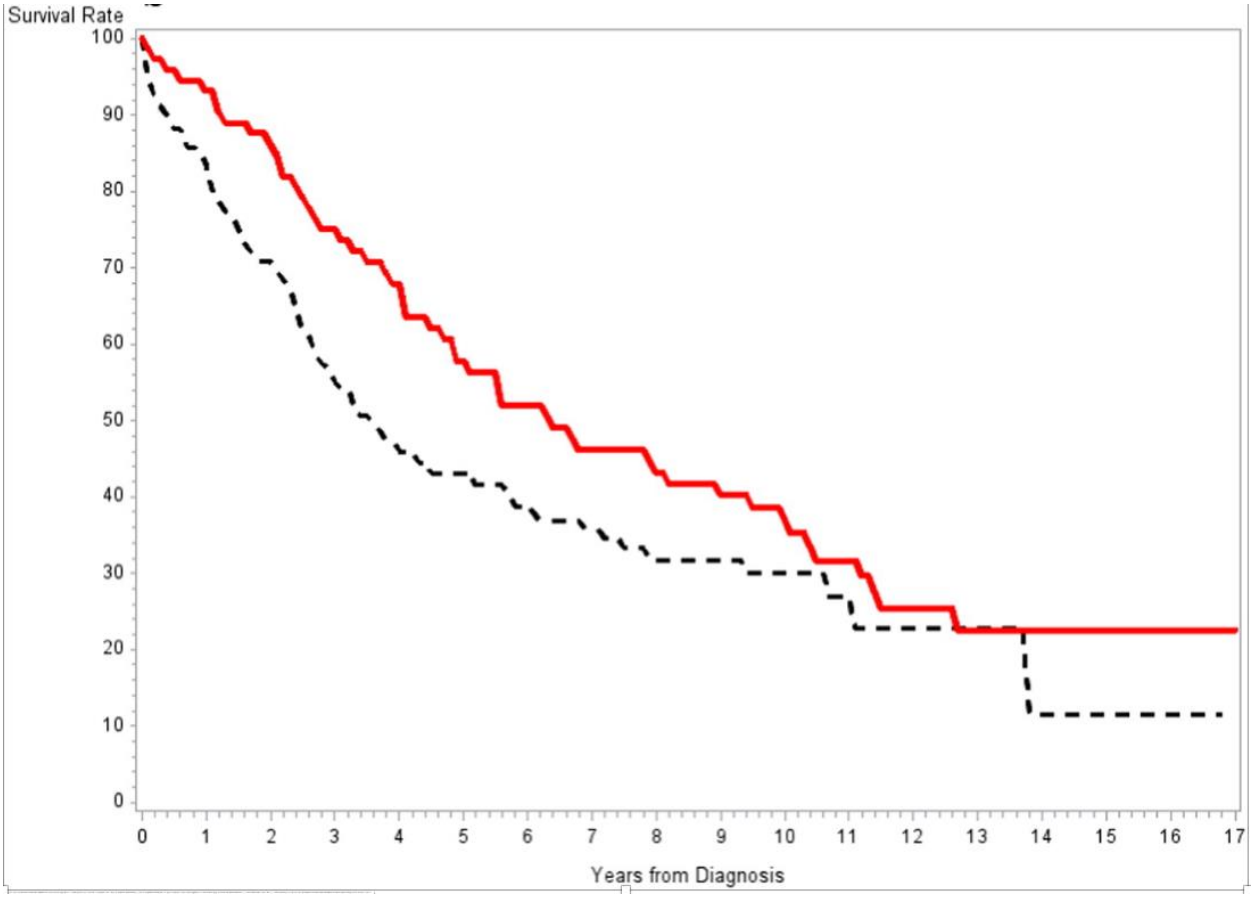


Fig. 2b) Ovarian cancer-specific survival by mode of detection in the intervention arm. Red (solid) line is for screen detected cases, black (dotted) line is for non-screen detected cases.

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?

If the red line did not really level off at 12 years, but instead continued declining like the dotted line, this would be more consistent with lead time bias, which increases survival only temporarily.

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?

It the red line levels off and the dotted line does not, this would be more consistent with overdiagnosis, in which the difference is not just due to earlier diagnosis, but to diagnosis of "cancers" that have a benign course.

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.