

Assessing lead time bias due to mammography screening on estimates of loss in life expectancy

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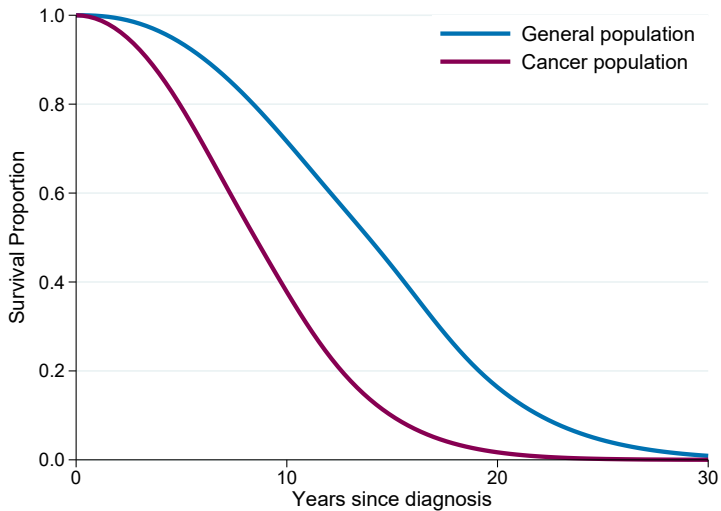
22nd August 2022

MEASURING CANCER PROGNOSIS

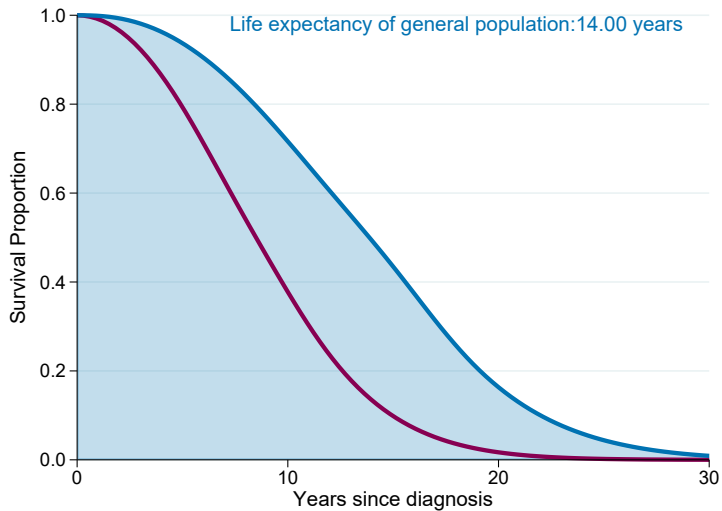
- Relative survival: the proportion of patients who are still alive at a specific timepoint in a hypothetical world where cancer is the only possible cause of death (net survival).
- Loss in life expectancy (LLE): the difference between the life expectancy of the **general population** (assumed to be free from the cancer of interest) and the life expectancy of the **cancer population** (with similar characteristics).
For individual i :

$$\text{LLE}(\mathbf{Z} = \mathbf{z}_i) = \int_0^{t_{max}} \mathbf{S}^*(t | \mathbf{Z}_1 = \mathbf{z}_{1i}) dt - \int_0^{t_{max}} \mathbf{S}(t | \mathbf{Z} = \mathbf{z}_i) dt$$

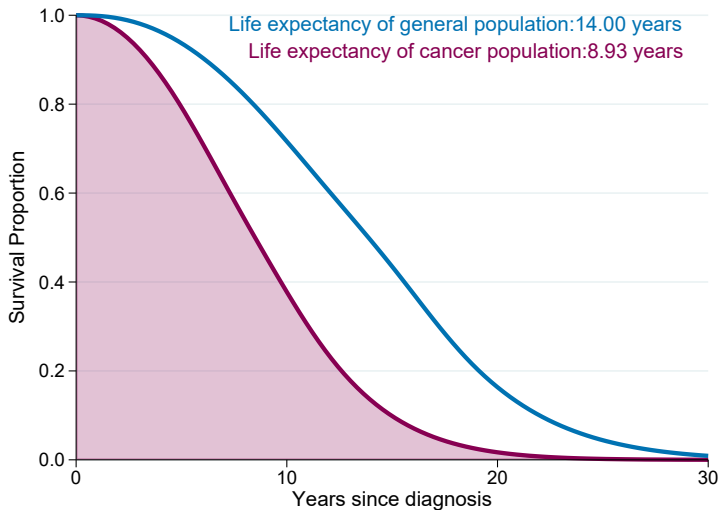
LOSS IN LIFE EXPECTANCY



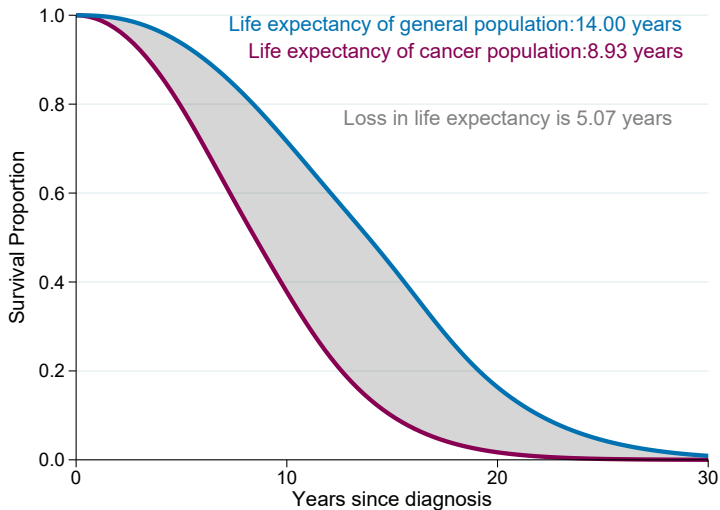
LOSS IN LIFE EXPECTANCY



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WHY USE LOSS IN LIFE EXPECTANCY?

- LLE is a real-world measure that captures the entire remaining lifespan.
- It can help us address useful questions:
 - Quantify the impact a cancer diagnosis has on a patient's life expectancy
 - Quantify disease burden in the society
 - “How many life-years are lost due to the cancer?”
 - “How many life-years are lost due to cancer by socioeconomic group?”

LLE ACROSS POPULATION GROUPS - SWEDEN

Age (years)	Education group	Life years lost (95%
		Study population
45	Low	9.90 (8.46,11.33)
	Medium	9.69 (8.76,10.62)
	High	9.11 (8.10,10.13)
55	Low	5.42 (4.85,5.99)
	Medium	5.27 (4.78,5.76)
	High	5.03 (4.52,5.54)
65	Low	2.81 (2.53,3.08)
	Medium	2.69 (2.44,2.93)
	High	2.86 (2.54,3.18)
75	Low	2.28 (2.12,2.44)
	Medium	1.89 (1.74,2.05)
	High	2.11 (1.88,2.33)

Bower H, Andersson TM-L, Syriopoulou E, Rutherford MJ, Lambe M, Ahlgren J, Dickman PW, Lambert PC. Potential gain in life years for Swedish women with breast cancer if stage and survival differences between education groups could be eliminated - Three what-if scenarios. *Breast* 2019, 45:75–81.

PROPORTION OF LIFE LOST (PLL)

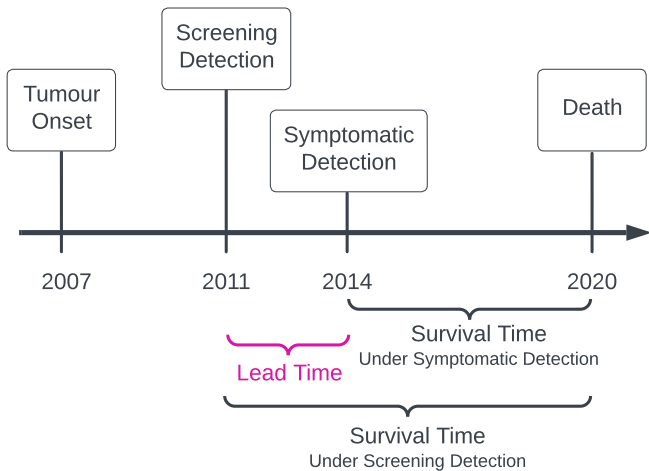
- Loss in life expectancy depends strongly on age.
- Using the proportional scale improves comparability across age groups:

$$\text{PLL}(\mathbf{Z} = \mathbf{z}_i) = \frac{\text{LLE}(\mathbf{Z} = \mathbf{z}_i)}{\int_0^{t_{max}} S^*(t | \mathbf{Z}_1 = \mathbf{z}_{1i}) dt}$$

MOTIVATION - WHY ARE THERE DIFFERENCES IN LLE?

- Many factors have been suggested as potential drivers for the observed differences e.g. stage at diagnosis, differential treatment, lifestyle, comorbidities, health-seeking behaviours, ...
- Screening (and lead time bias) may also drive part of the differences.
- The uptake of screening varies vary across socioeconomic groups, even in in countries where screening programmes are available on a national level.
- Are LLE estimates affected by lead time bias?

LEAD TIME



ASSESSING THE IMPACT OF LEAD TIME BIAS

- Screening can affect survival times through both real improvements in survival as well as **an artificial increase in survival times**.
- Partitioning the effect of screening into these two components is challenging as it would require knowledge of what would have happened in the absence of screening.
- We use a simulation-based approach informed by Swedish cancer registry data which uses a natural history model developed in a Swedish setting*.

*Andersson TM-L, Rutherford MJ, Humphreys K. Assessment of lead-time bias in estimates of relative survival for breast cancer. *Cancer Epidemiology* 2017, 46:50–56.

SIMULATION

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- tumour growth (and time at symptomatic detection) was simulated from a natural history model developed in a Swedish setting^{**}

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 - time to death due to other causes – from exponential distributions using mortality rates in the Swedish population lifetables stratified by sex, age and calendar year

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SCREENING SCENARIOS

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- Screening sensitivity
 - Low
 - Moderate
 - High
- Screening attendance
 - Perfect – everyone attends all screening visits
 - Imperfect
 - 80% of the individuals attend each scheduled screen visit with a probability of 0.9
 - 20% of the individuals attend each scheduled screen visit with a probability of 0.15

ESTIMANDS OF INTEREST

We run 200 simulations, and for each simulated dataset we obtained standardised estimates of

- 10-year relative survival
- Loss in life expectancy (LLE)
- Proportion on life lost (PLL)

for individuals diagnosed during years 1970–1974, both in the presence and in the absence of screening.

Estimates were standardised using the international cancer survival standards (ICSS) weights to match the age-distribution of a reference population (external standardisation) e.g. the externally age-standardised LLE:

$$\frac{1}{N} \sum_{i=1}^N w_i \times \widehat{\text{LLE}}(Z = z_i)$$

LEAD TIME BIAS

We compare

- estimates calculated in the absence of screening (*actual value*)
- estimates when screening is imposed

with the only difference that screen detected tumours result in an earlier diagnosis.

Screening might also result in improved survival outcomes of patients but here the actual survival time was not changed for screen detected cases.

- We want to isolate the impact of lead time bias!

DESCRIPTIVES - PROPORTION SCREEN DETECTED

Attendance	Screening	Number diagnosed	% screen detected	Lead time (mean)
Perfect	Low	2999 (2901 – 3098)	35.2 (33.7 – 37.1)	2.01 (1.83 – 2.22)
Perfect	Moderate	3028 (2925 – 3136)	45.1 (43.2 – 47.1)	2.45 (2.27 – 2.64)
Perfect	High	3062 (2959 – 3171)	53.0 (51.0 – 54.9)	2.98 (2.80 – 3.22)
Imperfect	Low	2988 (2887 – 3075)	27.1 (25.1 – 28.8)	1.98 (1.74 – 2.27)
Imperfect	Moderate	3010 (2904 – 3106)	35.3 (33.7 – 36.8)	2.42 (2.22 – 2.67)
Imperfect	High	3035 (2928 – 3143)	42.1 (40.6 – 44.0)	2.93 (2.71 – 3.19)

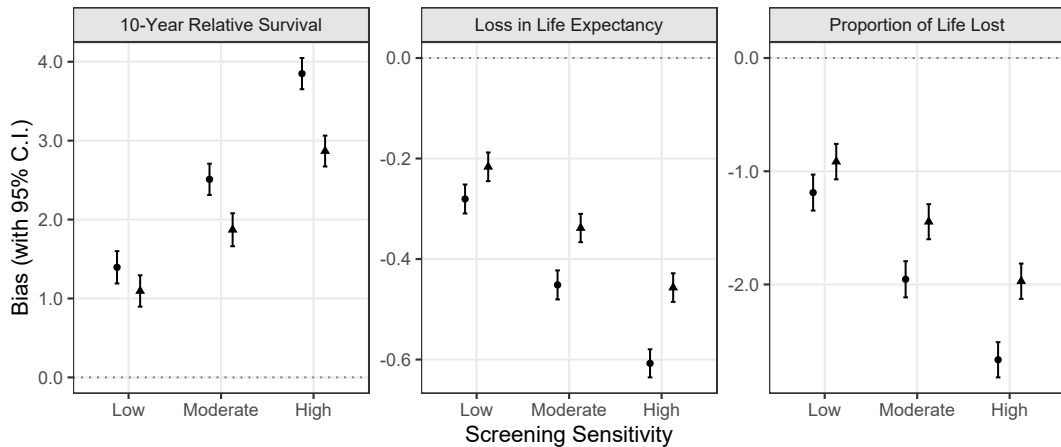
Averages (with 2.5 and 97.5 percentiles) based on 200 simulations

ESTIMATES 10-YEAR RS, LLE AND PLL

Attendance	Screening	10-Year RS	LLE	PLL
—	None	50.96 (48.18 – 54.04)	8.08 (7.62 – 8.50)	44.13 (41.58 – 46.39)
Perfect	Low	52.35 (49.36 – 55.44)	7.80 (7.37 – 8.20)	42.95 (40.56 – 45.13)
Perfect	Moderate	53.47 (50.72 – 55.91)	7.63 (7.24 – 8.00)	42.18 (39.95 – 44.21)
Perfect	High	54.81 (52.27 – 57.50)	7.48 (7.08 – 7.89)	41.47 (39.29 – 43.73)
Imperfect	Low	52.05 (49.29 – 54.91)	7.87 (7.45 – 8.29)	43.22 (40.84 – 45.56)
Imperfect	Moderate	52.83 (49.69 – 55.65)	7.74 (7.33 – 8.16)	42.69 (40.37 – 44.95)
Imperfect	High	53.83 (51.24 – 56.47)	7.63 (7.20 – 8.07)	42.16 (39.88 – 44.65)

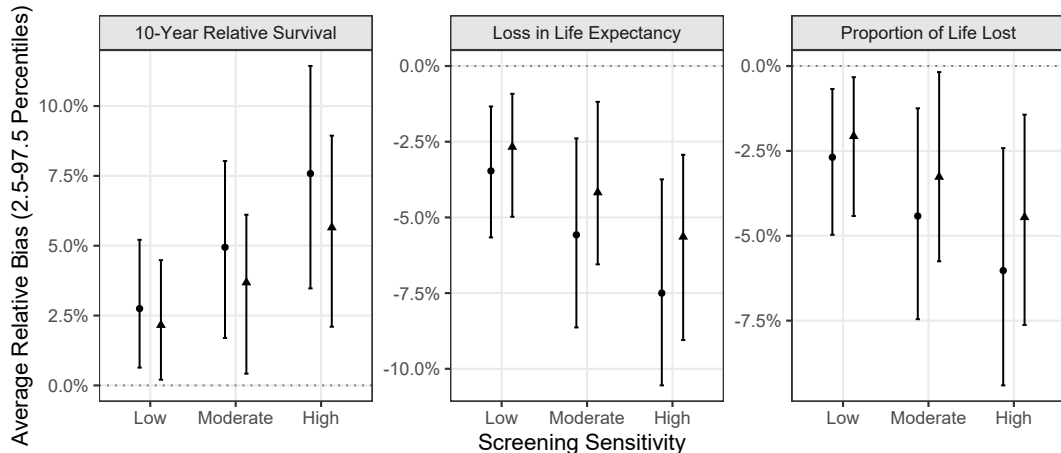
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BIAS



Attendance • Perfect ▲ Imperfect

RELATIVE BIAS



Attendance • Perfect ▲ Imperfect

CONCLUSIONS

- Lead time bias affects estimates of LLE and PLL.
- It is important to carefully consider the impact of lead time bias when reporting differences across population groups.
- A similar approach can be applied to other cancers, including cancers without screening programmes, but requires a tumour growth model for the cancer under study.

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 - Screening may lead in real improvements in survival. Here we only considered artificial improvements.

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- Our simulation is a simplification of the real world:
 - Screening may lead in real improvements in survival. Here we only considered artificial improvements.
 - We only considered invasive tumours; in practice some tumours will never lead to symptoms. We also didn't explore overdiagnosis.

FINAL REMARKS

- You can read more about this work at:
Syriopoulou E, Gasparini A, Humphreys K, Andersson T M-L, Assessing lead time bias due to mammography screening on estimates of loss in life expectancy. Breast Cancer Res 24, 15 (2022).
- All code is available at:
https://github.com/syriop-elisa/lead_time_bias