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

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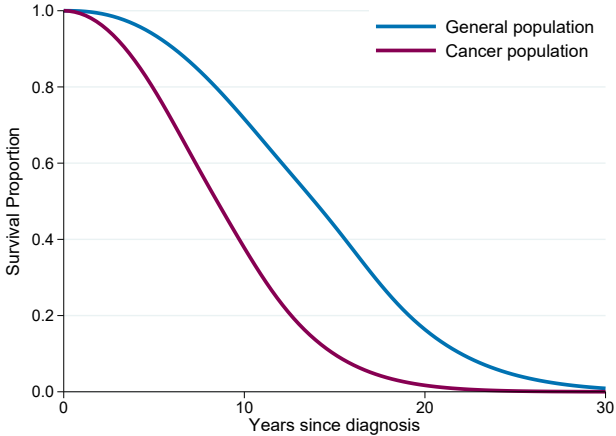
Measuring cancer prognosis

- 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 (that is assumed to be free from the cancer of interest) and the life expectancy of the cancer population (with similar characteristics). For individual i:

$$\mathrm{LLE}(\boldsymbol{Z} = \boldsymbol{z_i}) = \int_0^{t_{max}} \boldsymbol{S^*(t|Z_1 = z_{1i})}dt - \int_0^{t_{max}} \boldsymbol{S(t|Z = z_i)}dt$$

Loss in life expectancy



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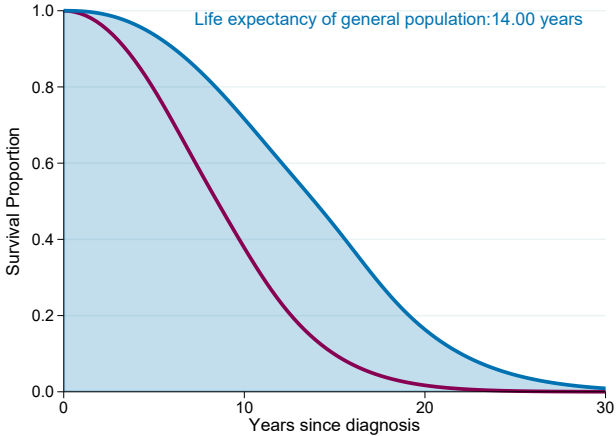

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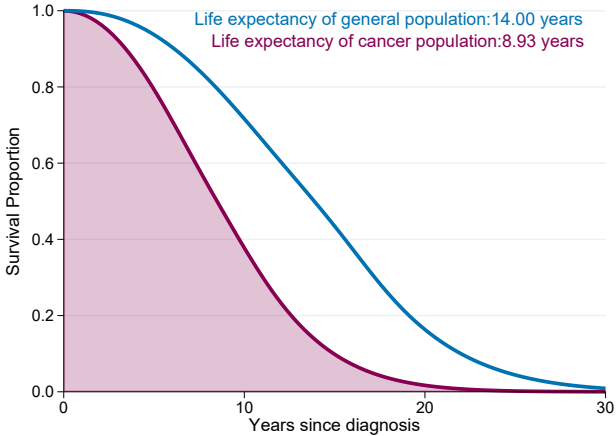

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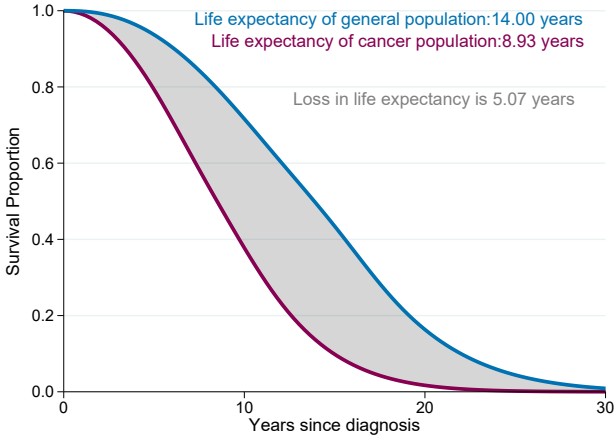
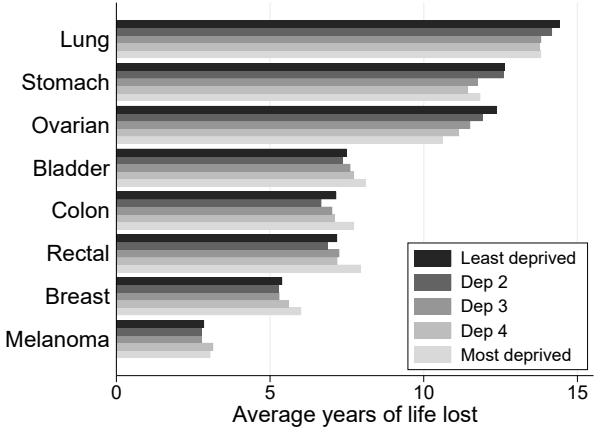


Why use loss in life expectancy?

- 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 e.g. "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 - England



Syriopoulou E, Bower H, Andersson TM-L, Lambert PC, Rutherford MJ. Estimating the impact of a cancer diagnosis on life expectancy by socio-economic group for a range of cancer types in England. Br J Cancer 2017, 117:1419–1426, https://doi.org/10.1038/bjc.2017.300

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, https://doi.org/10.1016/j.breast.2019.03.005

Proportion of life lost (PLL)

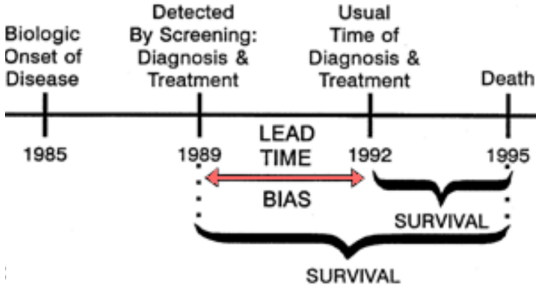
- Loss in life expectancy is a strongly age dependent measure.
- Using the proportional scale improves comparability across age groups:

$$\mathrm{PLL}(\boldsymbol{Z} = \boldsymbol{z_i}) = \frac{\mathrm{LLE}(\boldsymbol{Z} = \boldsymbol{z_i})}{\int_0^{t_{max}} S^*(t|\boldsymbol{Z_1} = \boldsymbol{z_{1i}})dt}$$

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



https://online.stat.psu.edu/stat507/lesson/10/10.6

- Lead time is the time between diagnosis of cancer via screening and the time that the cancer would have been diagnosed symptomatically in the absence of screening.
- Earlier detection results in prolonged survival times even when there are no actual improvements in survival.

Assessing the impact of lead time bias

- Screening can affect survival times both through real improvements in survival as well as 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*.

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Simulation

- Generated birth cohorts consisting of 10,000 individuals for every year between 1870 – 1965 (a fifth of the actual size of birth cohorts of females in Sweden).
- For each individual an age at breast cancer (tumour) onset was simulated based on incidence rates (by 5-year age groups) in Sweden from 1973 (the year before the introduction of mammography screening in Sweden).
- Only one tumour was allowed for every individual.

Simulation

For individuals with onset of breast cancer:

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

[**] Abrahamsson L and Humphreys K. A statistical model of breast cancer tumour growth with estimation of screening sensitivity as a function of mammographic density. Statistical Methods in Medical Research 2016, 25:1620–1637.

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

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Screaning scenarios

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  - Low
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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:

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

Lead time bias

We compare

- estimates calculated in the absence of screening (*true* 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)	44.14 (41.59 – 46.39)
Perfect	Low	52.35 (49.36 – 55.44)	7.80 (7.38 – 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 – 43.74)
Imperfect	Low	52.05 (49.29 – 54.91)	7.87 (7.45 – 8.29)	43.22 (40.84 – 45.57)
Imperfect	Moderate	52.83 (49.69 – 55.65)	7.75 (7.33 – 8.16)	42.69 (40.38 – 44.95)
Imperfect	High	53.83 (51.24 – 56.47)	7.63 (7.21 – 8.07)	42.17 (39.88 – 44.65)

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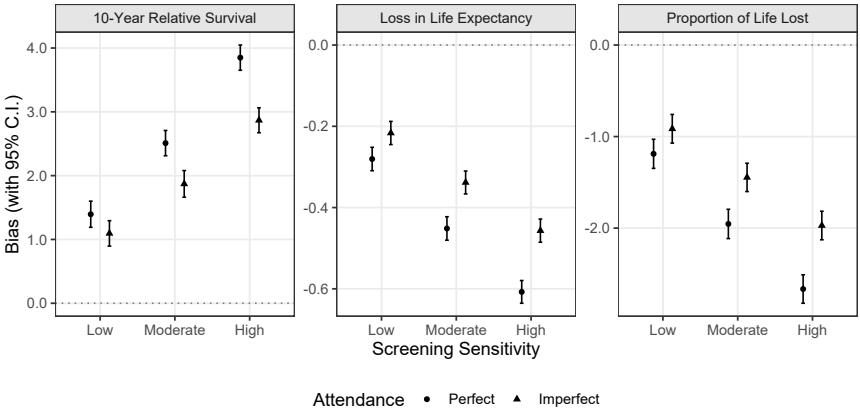
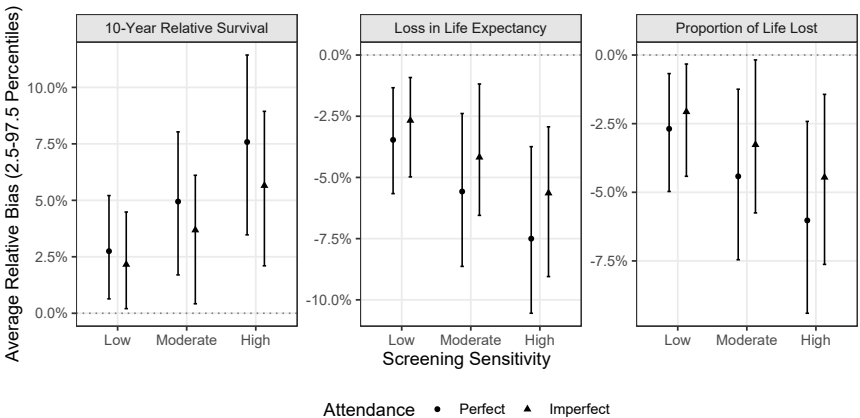
Bias


10-Year Relative Survival
Loss in Life Expectancy
Proportion of Life Lost
Bias (with 95% C.I.)
4.0
3.0
2.0
1.0
0.0
-0.2
-0.4
-0.6
-1.0
-2.0
Low
Moderate
High
Screening Sensitivity
Attendance
Perfect
Imperfect

Relative bias



Conclusions

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

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  - Screening may also result in real improvements in survival. Here we only considered artificial improvements.
  - We only compared “no screening” to screening scenarios; in practice there will be some screening attendance under both contrasting groups.
  - We only considered invasive tumours; in practice some tumours will never lead to symptoms. We also didn’t explore overdiagnosis.