An overview of measures for estimating cancer patient survival

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Outline

- About me
- Population-based data
- Competing events
- Measures of interest
  - Overall survival
  - Cause-specific survival
  - Relative survival
  - Crude probability of death
  - Loss in life expectancy

About me

- I studied mathematics and got a master in biostatistics in Greece.
- I did an internship at the University of Copenhagen as part of my master working in the area of survival analysis.
- Moved to the UK and worked at the University of Leicester focusing on statistical methods for cancer registry data.
- My PhD was on statistical methods to understand differences in cancer survival.
- Currently, I am a postdoc at Department of Medical Epidemiology and Biostatistics (MEB), Karolinska Institutet.
- Main research interests: survival analysis, statistical methods for cancer registry data, mediation analysis, relative survival framework, cancer disparities.

Population-based data

Population-based data include all patients diagnosed with cancer in a specific geographical region e.g Sweden.

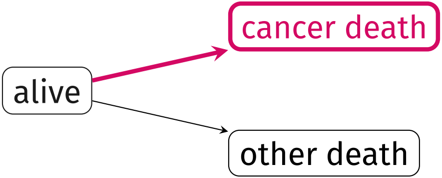
Such data are obtained by cancer registries that:

- have an important role in cancer surveillance and
- monitoring of temporal changes

There are three measures that are commonly estimated by cancer registry data: incidence, mortality in the population and survival among those diagnosed with cancer.

When interpreting trends in patient survival it is important to consider also incidence and mortality trends as well as clinical and biological insights.

Competing events



When investigating survival using cancer registry data, the event of interest is usually death due to a specific cancer.

However, other events that can potentially impede the occurrence of the event of interest may be present.

These types of events are known as competing events.

Measures of interest

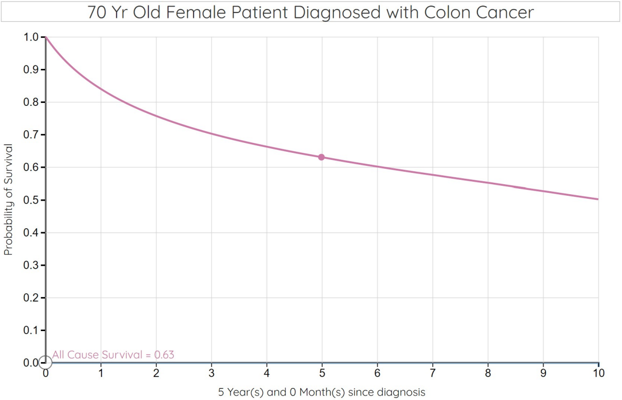
Based on the research question, we can choose either to accommodate or eliminate the competing events.

In the presence of competing events, we can estimate:

- Overall survival
- Cause-specific survival (net-setting)
- Relative survival (net-setting)
- Crude probability of death (real-world setting)
- Loss in life expectancy (real-world setting)

Overall survival

- Overall (all-cause) survival estimates the probability of remaining alive some time after diagnosis.
- The outcome is death from all causes.



https://interpret.le.ac.uk/

Overall survival

- Overall survival provides no information on survival associated with a cancer diagnosis.
- For instance, is low survival at 10 years after diagnsosis due to many deaths from other causes or many deaths from a colon cancer?

Cause-specific survival

- Deaths due to the cancer in question are considered to be events.
- The survival times of patients who die of other causes are censored.
- **Assumes that the classification on the cause of death is accurate**.

Potential issues with cause-specific survival

- The cause of death information obtained by cancer registries might not be reliable or is not available.
- Accurate coding is particularly problematic for older patients who are more prone to die from causes other than their cancer as well as patients with multiple tumours, rare cancers and as time since diagnosis increases*.
- Conceptual issues might also be present e.g. is death the result of cancer itself or a potential adverse event of the cancer treatment?

* Skyrud KD, Bray F, and Møller B. A comparison of relative and cause-specific survival by cancer site, age and timesince diagnosis. International Journal of Cancer, 1(135):196–203, 2014.

Excess mortality and relative survival

Don't require cause of death information.

Excess mortality

$$\text{excess mortality} = \text{all-cause mortality} - \text{expected mortality}$$

- It compares the all-cause mortality of the cancer population to the expected mortality of a comparable group in the general population.
- We obtain a measure of the excess mortality experienced by patients diagnosed with cancer, irrespective of whether the excess mortality is directly or indirectly attributable to the cancer (e.g includes mortality from treatment complications).

Excess mortality and Relative survival - II

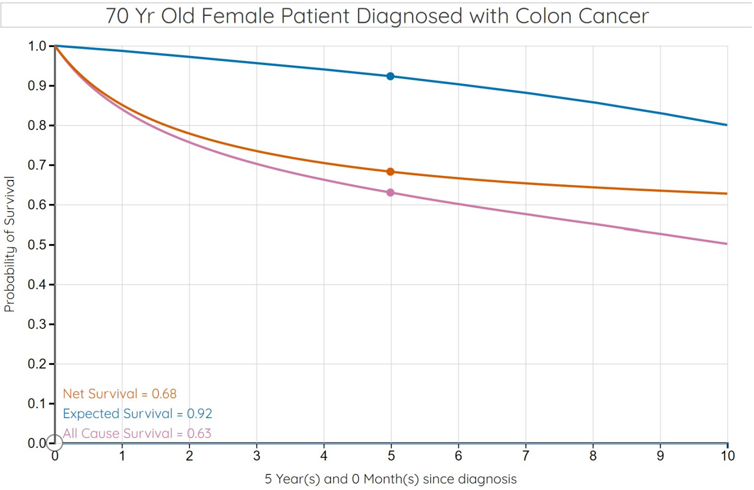
The survival analog of excess mortality is relative survival.

Relative survival

$$\text{relative survival} = \frac{\text{all-cause survival}}{\text{expected survival}}$$

- The expected survival proportion is considered to be known and is usually obtained by available population lifetables.
- These are often nationwide population lifetables stratified by factors such as age, sex, calendar time etc.

Example - colon cancer, Sweden



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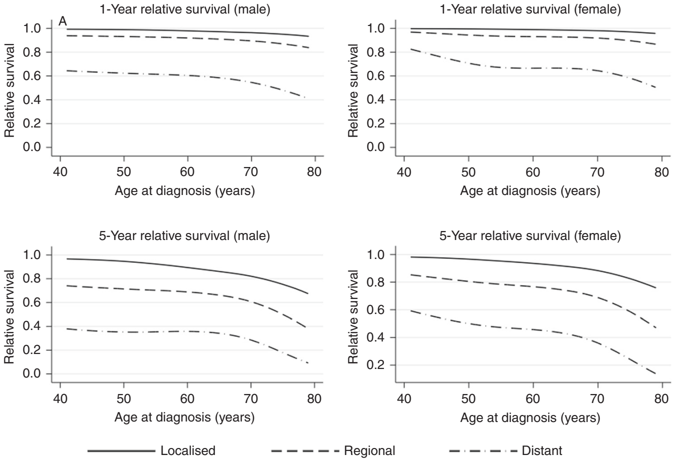
Expected survival

- **It is important to have sufficiently stratified population lifetables**, so that the cancer population and the general population have similar characteristics and their only difference is the cancer under study.
- If this is not the case, then our estimates are biased.
- For example, patients with smoking-related cancers will experience excess mortality, compared to the general population, due to both the cancer and other smoking-related conditions.

Net survival

- When appropriate expected survival probabilities exist, then relative survival estimates *net survival*.
- Net survival is survival in a hypothetical world where the cancer of interest is the only possible cause of death.
- This interpretation might sound not ideal, but it makes net survival a very useful measure for comparing cancer survival across groups/countries.
- Independent of background mortality so we can make comparisons across time, across different subgroups in our population or across different countries.

Example - melanoma, SEER data



Smith AJ, Lambert, PC, Rutherford, MJ. Understanding the impact of sex and stage differences on melanoma cancer patient survival: a SEER-based study. Br J Cancer 2020, https://doi.org/10.1038/s41416-020-01144-5.

Example - ICBP SURVMARK-2

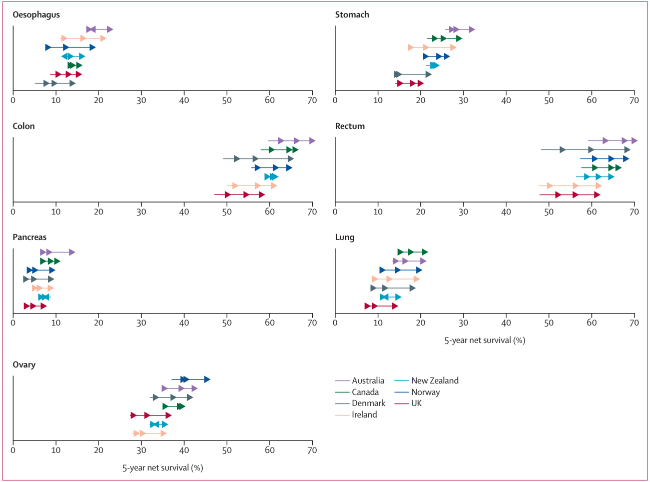
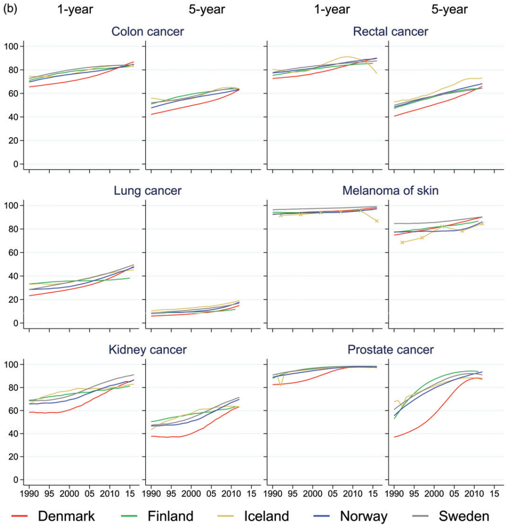


Figure 1: Age-standardised 5-year net survival by site, country, and period of diagnosis, 1995–2014

Arnold M, Rutherford MJ, Bardot A et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. Lancet Oncol 2019, 20(11):1493-1505.30456-5

Example - Nordic countries



Lundberg FE, Andersson TM-L, Lambe M et al. Trends in cancer survival in the Nordic countries 1990–2016: the NORDCAN survival studies. Acta Oncol 2020, 59:11, 1266-1274, https://doi.org/10.1080/0284186X.2020.1822544

Cause-specific survival vs relative survival

- Cause-specific survival assumes accurate classification of cause of death.
- Relative survival requires that there is appropriate information on expected survival.
- Both measures try to estimate net survival.
- Choice should be made based on which one is the most resonable assumption for our setting.

Net setting

Net survival:

- useful for comparing survival between different populations such as countries or socioeconomic groups as it is not affected by background mortality (i.e. mortality due to other causes).
- It can also be a measure of great interest for studying the aetiology of a disease or temporal trends.

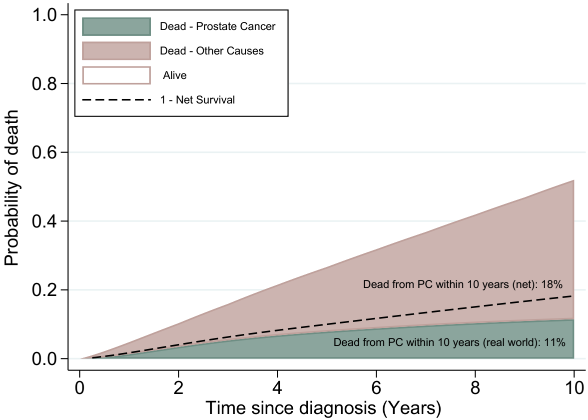
However, net survival refers to a hypothetical world.

What statistics are useful for healthcare professionals and patients?

Real-world setting

- Patients and healthcare professionals seek information that allows them to understand or to communicate the prognosis associated with a specific cancer.
- Measures that aknowledge the risk from competing events are more informative than net survival.
- Such measure is the crude probabity of death due to cancer in a real-world setting where other causes of death are present.
- Also useful for policy decisions e.g. on resource allocation.

Net vs crude probability of death - example

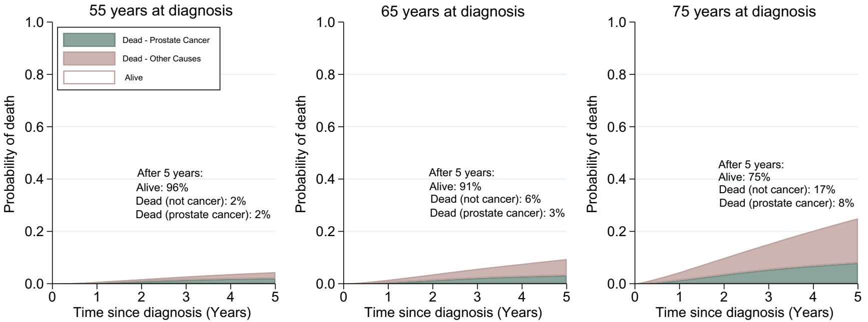


Eloranta S, Smedby KE, Dickman PW, Andersson TM. Cancer survival statistics for patients and healthcare professionals – a tutorial of real-world data analysis. J Intern Med 2020, https://doi.org/10.1111/joim.13139

Crude measures - 'real world' setting

- Crude measures accommodate competing events and refer to a setting where both cancer and other causes of death are present (as opposed to a hypothetical world).
- The crude probability of death from cancer is lower than the net probability of death due to cancer, since some patients will die due to other causes.
- Similarly, the cancer-specific survival in the presence of competing events is often higher than cancer-specific survival in the absence of competing events.

Crude probability of death

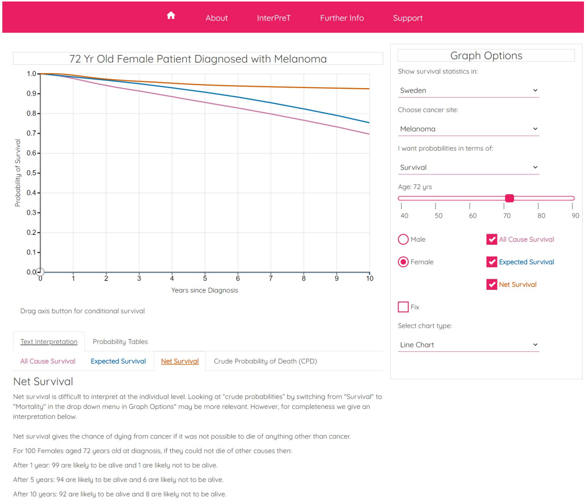


Older patients have a higher risk of death due to other causes.

Eloranta S, Smedby KE, Dickman PW, Andersson TM. Cancer survival statistics for patients and healthcare professionals – a tutorial of real-world data analysis. J Intern Med 2020, https://doi.org/10.1111/joim.13139

WEBTOOL - INTERPRETATION OF CANCER MEASURES

https://interpret.le.ac.uk/

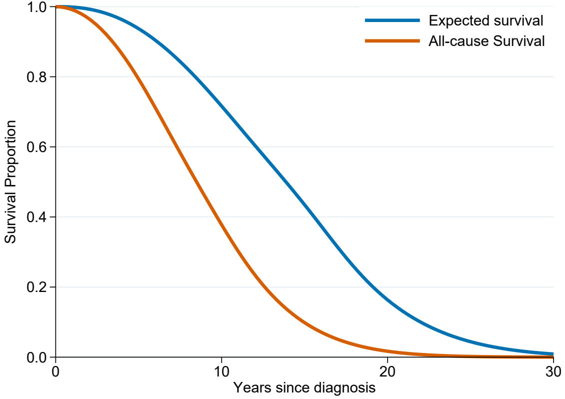


Loss in life expectancy

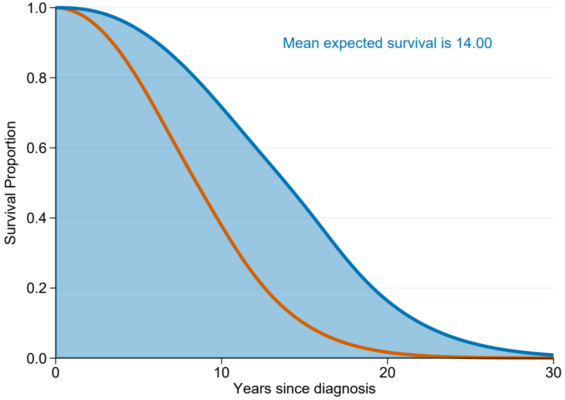
- It might be useful to know more than only the proportion survived at a specific time.
- Loss in life expectancy (LLE) is a real-world measure that looks over the whole of life expectancy*.
- LLE is defined as the difference between the life expectancy in the cancer population and the general population (with similar characteristcs).

* Andersson TM-L, Dickman PW, Eloranta S, Lambe M, Lambert PC. Estimating the loss in expectation of life due to cancer using flexible parametric survival models. Statistics in Medicine, 32:5286–5300, 2013.

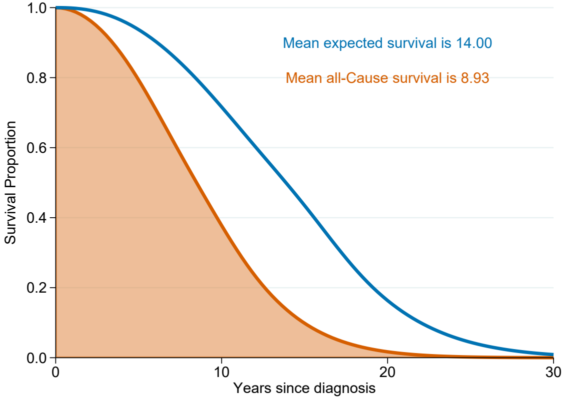
Loss in life expectancy



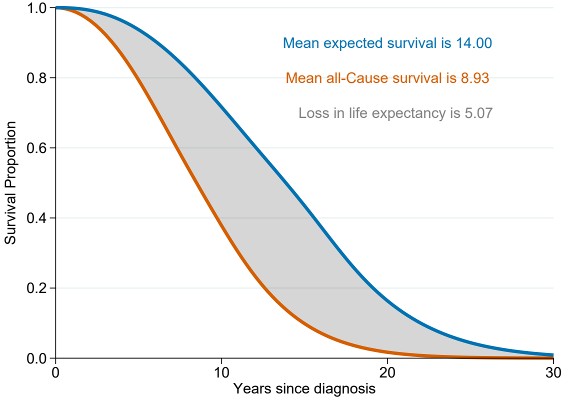
Loss in life expectancy



Loss in life expectancy



Loss in life expectancy

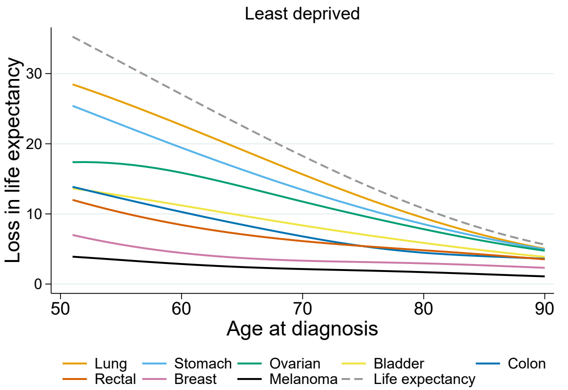


Why use loss in life expectancy?

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 disease?"

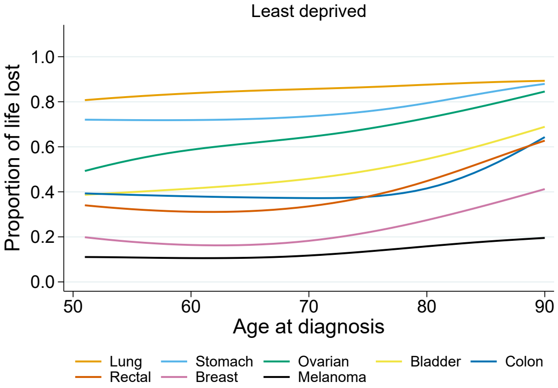
Example - LLE by cancer in England



Loss in life expectancy is a highly age dependent measure.

Syriopoulou E, Bower H, Andersson, TL et al. 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

Example - Proportion life lost by cancer in England



Using the proportional scale improves comparability across ages.

Syriopoulou E, Bower H, Andersson, TL et al. 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

Exploring survival differences

- Survival after a cancer diagnosis varies considerably across population groups e.g between socioeconomic groups.
- **Is there a third variable that can partly explain these differences?**
- Could stage at diagnosis partly explain the survival differences between the least and most deprived groups?
- Understanding which factors drive differences is very important.
- For example, if survival differences across deprivation groups are largely driven by differences in stage at diagnosis, then policies could be implemented to encourage earlier detection in the most deprived groups.
- Mediation analysis methods allow the exploration of such questions*.

*Syriopoulou E, Rutherford MJ, Lambert, PC. Understanding disparities in cancer prognosis: An extension of mediation analysis to the relative survival framework. Biometrical Journal 2021; 63: 341– 353.

Summary

- There are a lot of different measures to estimate cancer patient survival.
- Relative survival refer to net setting and account for differences in background mortality. It can be useful for comparing the cancer impact across populations groups.
- Crude probabilities of death refer to a real-word setting and are more useful for communiting prognosis to patients and clinicians.
- LLE measures refer to a real word setting and have a more intuitive interpretation. Also look over the whole of the remaining timespan.
- Every measure helps us understand a different aspect of the cancer's impact.
- Which method to use depends on the research question and the target audience.