Is categorising cancer stages as I-IV too crude?

A microsimulation study on breast cancer survival, socioeconomic position and stage at diagnosis.

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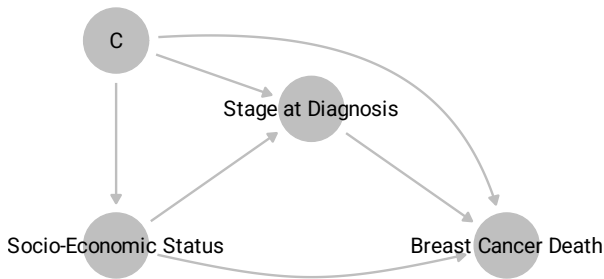
Background

- In cancer studies we may perform causal mediation analysis to explore the reasons behind survival differences between subgroups.
- For instance, are survival differences by socio-economic position mediated by tumour stage?



Is categorising cancer stages as I-IV too crude?

- Typically, we use cancer stages I-IV to define tumour stage.
- Cancer stages (I–IV) are based on tumour size (T), lymph node involvement (N), and distant metastases (M).
- Is staging I-IV adequate or does it result in substantial within-group heterogeneity in survival outcomes?
- We wanted to explore the impact of ill-defined mediators (like crude staging) on the estimation of mediated effects.

A microsimulation experiment

- We performed a microsimulation.*
- We generated birth cohorts of women according to a breast cancer natural history model developed in Swedish settings.
- We independently simulated socio-economic position and imposed a screening programme mimicking that in Sweden.
- We do not consider non-invasive (in situ) cancers and we do not simulate spread to distant metastasis (for simplicity): thus, we can only observe stages I-III.

*A similar approached is described in Syriopoulou E, Gasparini A, Humphreys K, Andersson TML. Assessing lead time bias due to mammography screening on estimates of loss in life expectancy. Breast Cancer Research. 2022;24(1)

Microsimulation scenarios

We design the following simulation scenarios, assuming that between socioeconomic groups there are:

I. No differences in terms of rate of symptomatic detection and screening attendance.

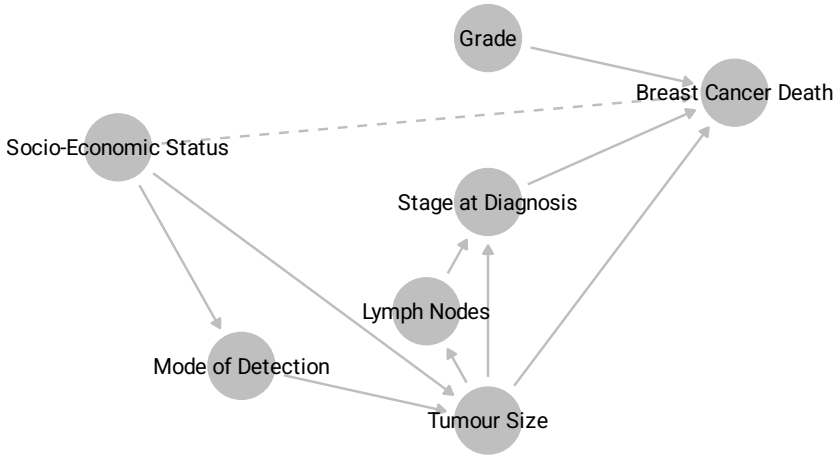
II. Different rates of symptomatic detection.

III. Different probabilities of attending each screening visit.

IV. Both different rates of symptomatic detection and probabilities of attending each screening visit.

Across all scenarios, we assume no direct effect of socioeconomic position on breast cancer survival.

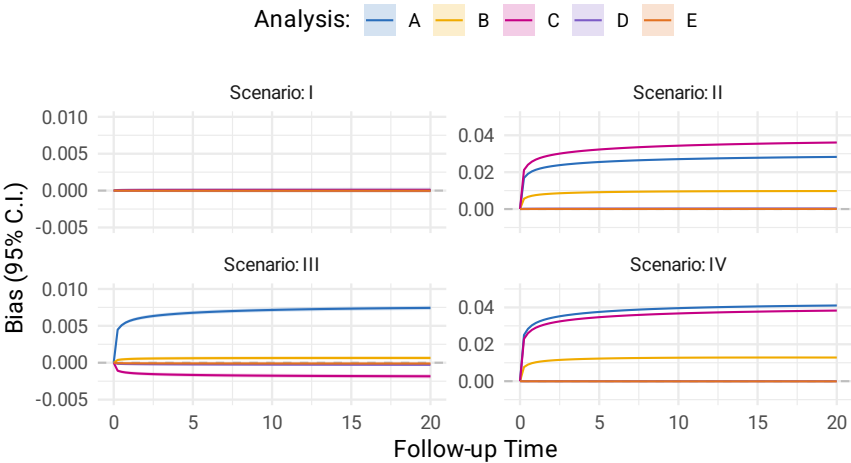
Illustration of the data-generating model



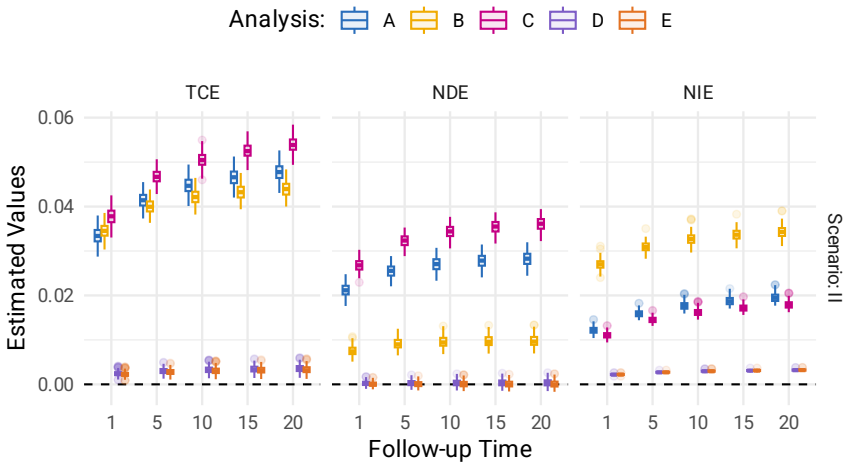
Analysis strategies

Analysis	Survival Model Covariates	Stage Definition
A	Age, SES, Grade, Stage	Standard (I-III)
B	Age, SES, Grade, Stage	T-N-M Product
C	Age, SES, Grade, Stage, Detection Mode	Standard (I-III)
D	Age, SES, Grade, Stage, Tumour Diameter	Standard (I-III)
E	Age, SES, Grade, Stage, Detection Mode, Tumour Diameter	Standard (I-III)

Results


Analysis:
A
B
C
D
E
Scenario: I
Scenario: II
Scenario: III
Scenario: IV
Bias (95% C.I.)
0.010
0.005
0.000
-0.005
0.04
0.02
0.00
0
5
10
15
20
Follow-up Time

Results


Analysis: A B C D E
TCE
NDE
NIE
Estimated Values
0.06
0.04
0.02
0.00
1 5 10 15 20
Follow-up Time
Scenario: II

Conclusions

- Using crude staging (I–III) introduced bias, up to a 4%, despite no true differences.
- A more detailed stage (T × N × M) reduced bias, but didn't fully eliminate it.
- Adjusting for mode of detection (screening vs. symptomatic) did not remove the bias.
- Adjusting for tumor size minimized bias in the direct effect but also led to near-zero estimates for the total causal difference.
- If interest is on both direct and indirect effects, detailed TNM staging can reduce underestimation of the indirect effect.
- When adjusting for stage, the estimated direct effect may still include some stage-related effects if too crude.