

Survival differences between socioeconomic groups of colon cancer patients: exploring the role of stage at diagnosis using mediation analysis

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Survival after a cancer diagnosis varies considerably across population groups e.g socioeconomic groups.

Deprivation Group	5-year RS	Mean Years w/o Cancer	Mean Years with Cancer	Prop (%)	
Age at diagnosis: 7	Age at diagnosis: 70				
Least deprived	63.6	18.3	11.4	37.7	
2	62.3	17.4	10.7	38.5	
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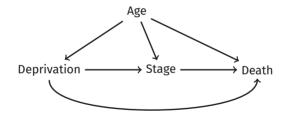
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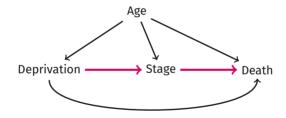
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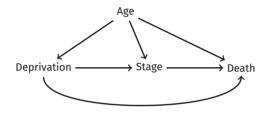
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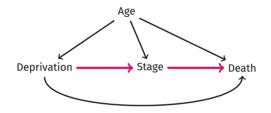
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Mediation analysis into the relative survival framework can be a valuable tool!

PARTITIONING THE TOTAL RELATIVE SURVIVAL DIFFERENCE

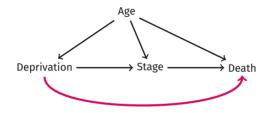


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Natural direct effect: quantifies the differences in relative survival that are not due to stage differences

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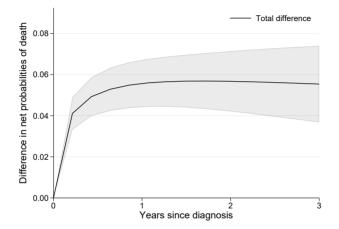
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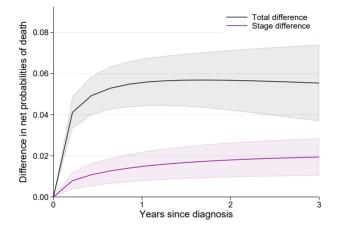
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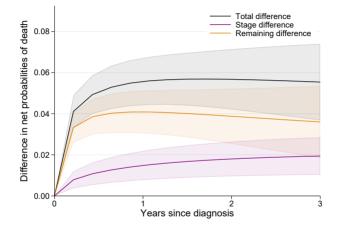
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- To obtain 95% confidence intervals parametric bootstraps of 200 iterations were performed for each imputed dataset.



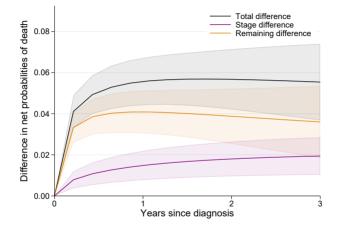
At 3-years after diagnosis, the total difference is **5.5** percentage points.



From the total difference, **1.9** percentage points are due to stage differences.



From the total difference, the remaining 3.6 percentage points are due to other factors.



At 3-years after diagnosis, stage explains **35%** (=1.9/5.5) of the total differences.

MOVING TO A REAL-WORLD SETTING

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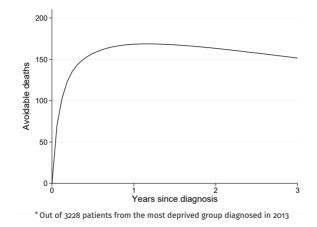
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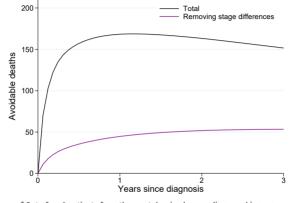
How many "avoidable deaths" would there be if the most deprived had the same stage distribution as the least deprived?

AVOIDABLE DEATHS WHEN REMOVING STAGE DIFFERENCES



At 3-years after diagnosis, there are 151 total avoidable deaths:

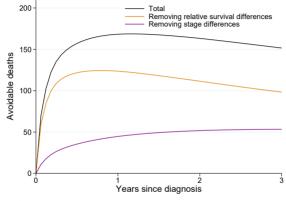
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 - For example, if survival differences across deprivation groups are largely driven by differences in stage at diagnosis, then policies could be implemented to encourage earlier detection in the most deprived groups.
- Mediation analysis into the relative survival framework provides an opportunity to answer these complex questions.

SELECTED REFERENCES

- Pohar Perme M, Stare J & Estève J On Estimation in Relative Survival. *Biometrics*,, 68, 113-120, 2012.
- Royston P & Lambert P C Flexible parametric survival analysis in Stata: Beyond the Cox model. Stata Press, 2011.

Syriopoulou E, Rutherford M J & Lambert, P C Marginal measures and causal effects using the relative survival framework. International Journal of Epidemiology, 49, 619–628, 2020.

Syriopoulou E, Rutherford M J & Lambert, P C Understanding disparities in cancer prognosis: An extension of mediation analysis to the relative survival framework. *Biometrical Journal*, in press, 2020.