

Early Detection of Triple-Negative Breast Cancer: Evidence of a Favorable Prognostic Impact in a Comparative Analysis of Screen-Detected versus Symptomatic Cases

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APPENDIX A

The role of mediators in the association between detection method and survival outcomes.

Rationale:

We conducted a mediation analysis in order to test the hypothesis that the detection method has an impact on survival outcomes through the presence of mediators. In particular, we considered stage at diagnosis and vascular invasion as potential mediators, since it is well recognized that screening best identifies breast cancers with a lower stage at diagnosis and with favourable biologic features, which are known factors strongly associated with a better prognosis [1][2][3]. Hence, we hypothesized that the better survival outcomes of screen-detected lesions could be, at least partially, mediated by a lower proportion of screen-detected cancers diagnosed at an advanced stage and with the presence of vascular invasion.

Methods

To assess whether the stage at diagnosis and vascular invasion played the role of mediators in the association between the method of detection and disease-free survival (DFS), and between screen detection and overall survival (OS), mediation analyses were conducted, adjusting the estimates for the same variables included in the Cox models described in the main paper: age at diagnosis, neoadjuvant chemotherapy, adjuvant chemotherapy, type of surgery, histologic type, histologic grade, Ki-67 and tumor-infiltrating lymphocytes (TILS).

In particular, we employed an innovative approach based on VanderWeele's counterfactual method [4]. This advanced statistical tool enabled us to disentangle the Total Effect (TE) of screen detection on the outcomes into two distinct components: the Pure Direct Effect (PDE), which captures the effect of the exposure on each outcome that is not mediated by the mediators, and the Total Indirect Effect (TIE), which represents the effect of exposure on the same outcome that is mediated through the identified mediators. The confidence intervals were calculated as 95% bootstrap CIs using the percentile method. Prior to applying this technique, we ensured that the underlying assumptions of the method were satisfied. Specifically, preliminary analyses were conducted using multivariable logistic, multinomial and Cox Proportional Hazards regression models, when appropriate, to assess the associations between exposure-mediator and mediator-outcome.

Results

The results related to the mediation analyses are shown in Table 1, Figure 1 and Figure 2, while the analyses carried out to check the assumptions underlying the mediation approach are presented in Table 2 and Table 3.

Focusing on DFS, the HR estimates suggest that method of detection is not directly associated with DFS (HR 1.29 95% CI 0.91-2.02), while stage at diagnosis and vascular invasion appear to act as mediators of this association, although the estimates are at the limits of significance (HR 1.18, 95% CI 0.98-1.43). Additionally, the overall TE was found to be statistically significant (HR 1.52, 95% CI 1.01-2.40). In contrast, considering OS, none of the estimates were statistically significant.

These findings are confirmed by Figure 3 and Figure 4, which illustrate how the HR estimates related to PDE, TIE and TE evolve over the follow-up period considered in this study.

These results may be influenced by the small sample size, the presence of missing information for several variables and the short follow-up time, so it is difficult to draw certain conclusion from this limited evidence. However, the results of this preliminary analysis show that stage at diagnosis and vascular invasion are likely to act as mediators in the associations between screen detection and disease-free survival, while the evidence is more limited regarding the association between screen detection and overall survival.

Further research is therefore needed to understand more precisely the complex interaction between the factors responsible for the better survival outcomes of screen-detected cases.

Variable	Category	DFS	OS
		HR (95% CI)	HR (95% CI)
PURE DIRECT EFFECT			
Method of detection	Screen detected	Ref	Ref
	Symptomatic	1.29 (0.91-2.02)	1.23 (0.75-2.10)
TOTAL INDIRECT EFFECT			
Stage at diagnosis and vascular invasion	Screen detected	Ref	Ref
	Symptomatic	1.18 (0.98-1.43)	1.16 (0.97-1.49)
TOTAL EFFECT			
Method of detection	Screen detected	Ref	Ref
	Symptomatic	1.52 (1.01-2.40)	1.44 (0.86-2.39)

Table 1. Mediation analyses of method of detection on DFS or OS, considering stage at diagnosis and vascular invasion as mediators of these associations. Age at diagnosis, neoadjuvant chemotherapy, adjuvant chemotherapy, type of surgery, histologic type, histologic grade, Ki-67 and tumor-infiltrating lymphocytes (TILS) were considered as confounding variables.

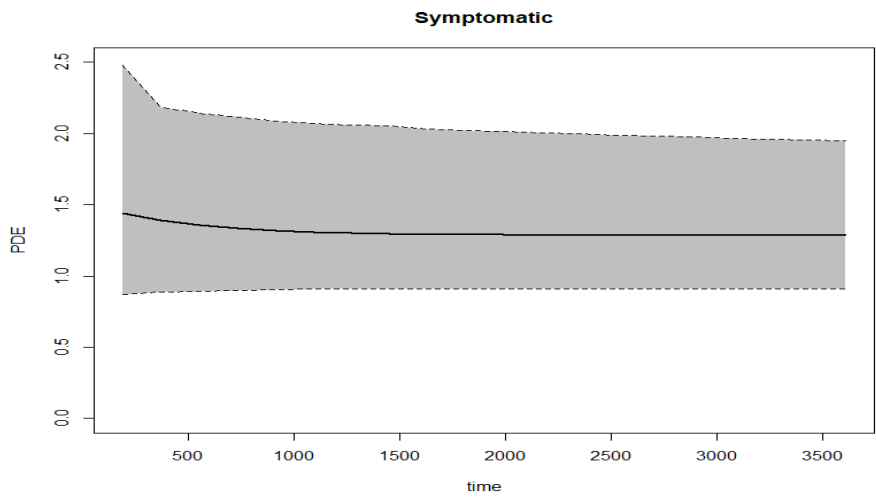
Variable	Category	DFS	OS
Exposure-Mediator			
		OR (95%CI)	OR (95%CI)
Method of detection	Screen detected	Ref	Ref
	Symptomatic	3.33 (1.98-5.76)	3.33 (1.98-5.76)
Mediator-Outcome			
		HR (95%CI)	HR (95%CI)
Stage at Diagnosis	I-II	Ref	Ref
	III-IV	3.63 (2.34-5.63)	3.33 (1.96-5.64)

Table 2. Association between mediator-exposure and outcome-mediator, conducted through multivariable logistic regression and Cox Proportional Hazards Models, considering stage at diagnosis as mediator.

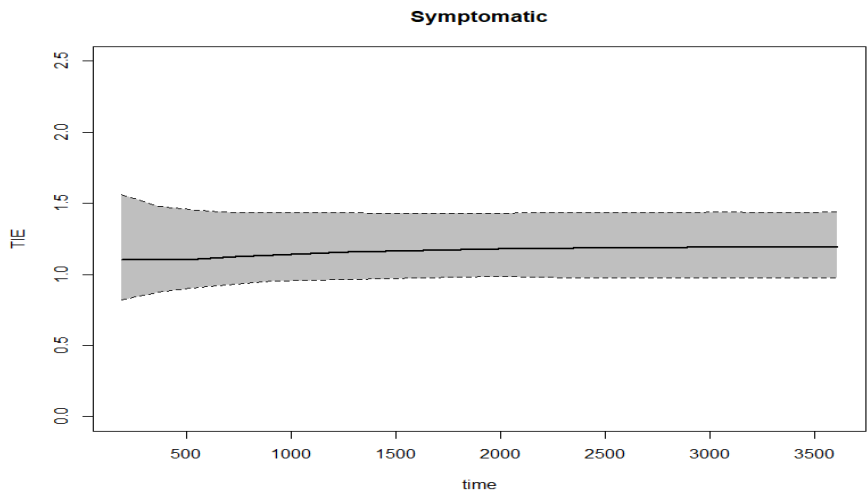
Variable	Category	DFS	OS
Exposure-Mediator			
		OR (95%CI)	OR (95%CI)
Method of detection	Screen detected	Ref	Ref
	Symptomatic	1.37 (0.88-2.15)	1.37 (0.88-2.15)
Mediator-Outcome			
		HR (95%CI)	HR (95%CI)
Vascular invasion	No	REF	REF
	Yes	3.28 (1.94-5.55)	2.96 (1.60-5.57)

Table 3. Association between mediator-exposure and outcome-mediator, conducted through multivariable logistic regression and Cox Proportional Hazards Models, considering vascular invasion as mediator.

a) Pure Direct Effect (PDE)



b) Total Indirect Effect (TIE)



c) Total Effect (TE)

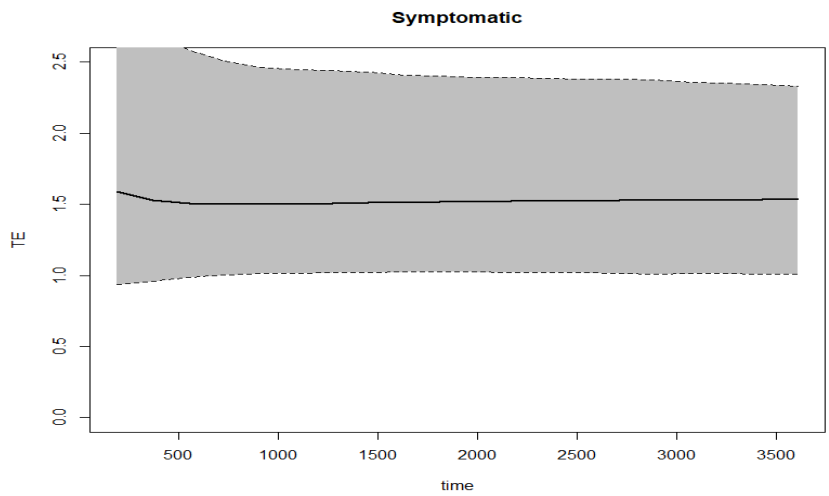
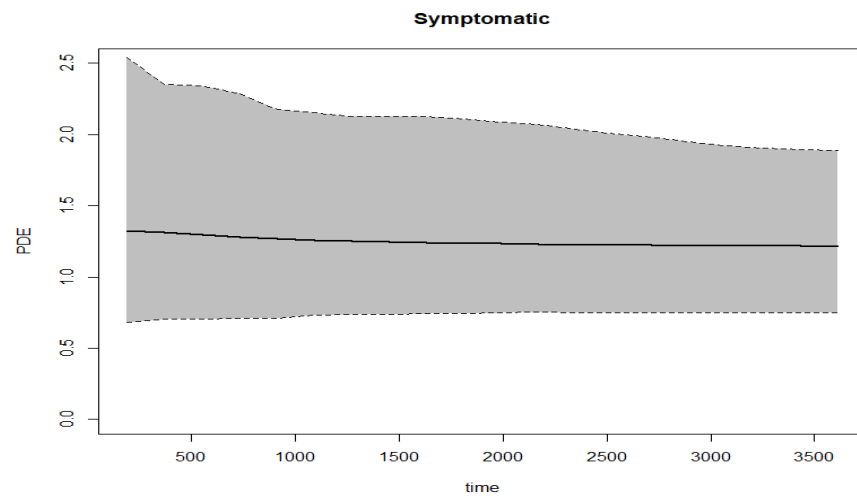
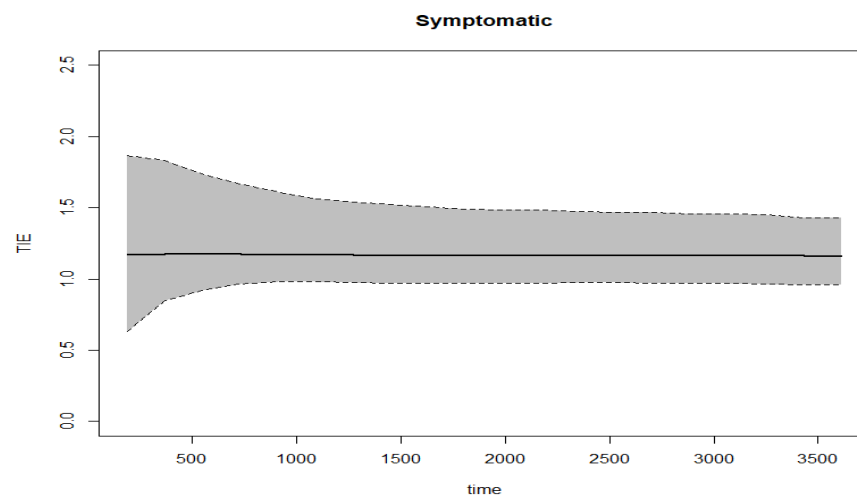


Figure 1. Pure Direct Effect (PDE), Total Indirect Effect (TIE), and Total Effect (TE) over time related to the outcome DFS

a) Pure Direct Effect (PDE)



b) Total Indirect Effect (TIE)



c) Total Effect (TE)

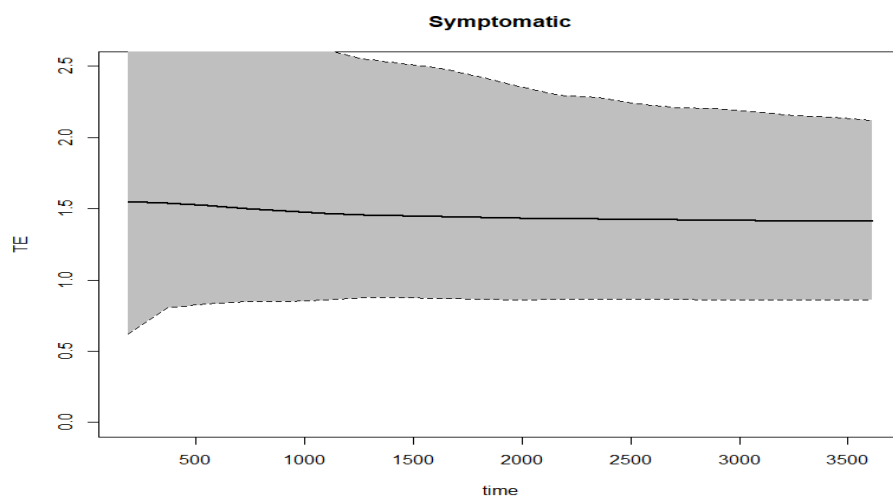


Figure 2. Pure Direct Effect (PDE), Total Indirect Effect (TIE), and Total Effect (TE) over time related to the outcome OS

References

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