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# Conflict of Interest Disclosure

- The speaker has nothing to declare.

# Normal tissue genetically-adjusted radiation dose (NT_GARD) for causal inference models of late toxicity after breast cancer radiotherapy

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**Aim**: to define a normal tissue genetically adjusted radiation dose (NT_GARD) integrating individual genetic radiosensitivity to the delivered physical dose to the breast (EQD2MaxD)

**Cohort**: 1823 REQUITE breast cancer patients

**Outcome**: CTCAE grade≥2 fibrosis (13%)

1 Modelling genetic susceptibility → 2 Modelling NT_GARD → 3 Causal framework for late fibrosis

## Modelling genetic susceptibility

127 SNPs already associated with side effects after BC RT in literature

*Association with late fibrosis*

The top 30 contributing SNPs were selected for inclusion in the PRS

*Cox-multivariable prediction*

$$PRS(pts_i) = \sum_{j=1}^{30} \beta_j * SNP_j$$

## Modelling NT_GARD

NT_GARD was derived from a Cox model including PRS and EQD2MaxD, according to the formula:

$$NT\_GARD = EQD2MaxD + \frac{\beta_{PRS}}{\beta_{EQD2MaxD}} \cdot PRS$$

- $EQD2MaxD$ = patient-specific maximum dose to the breast
- $\frac{\beta_{PRS}}{\beta_{EQD2MaxD}} \cdot PRS$ = individualised genetic contribution on the effectiveness of the dose

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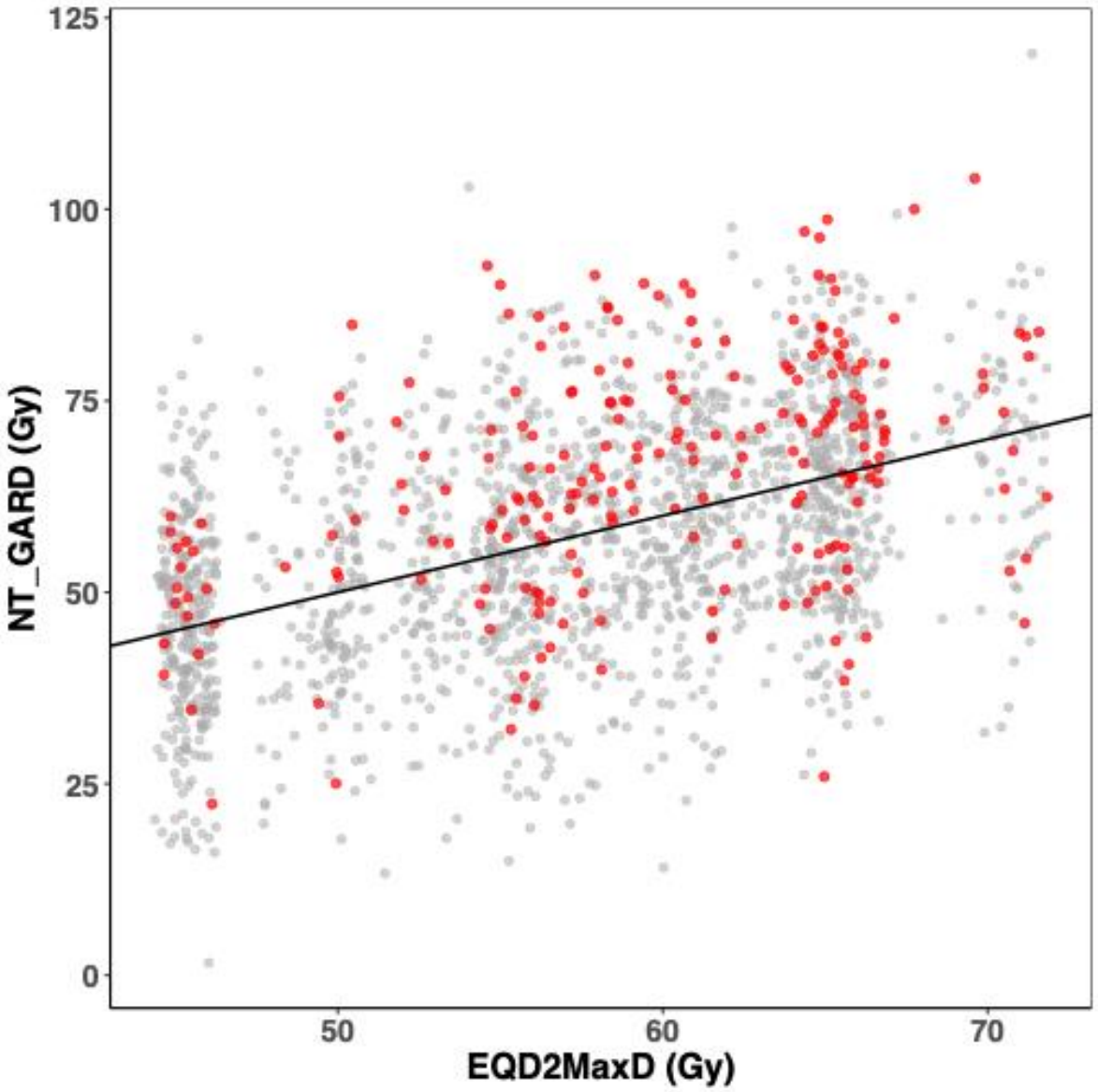
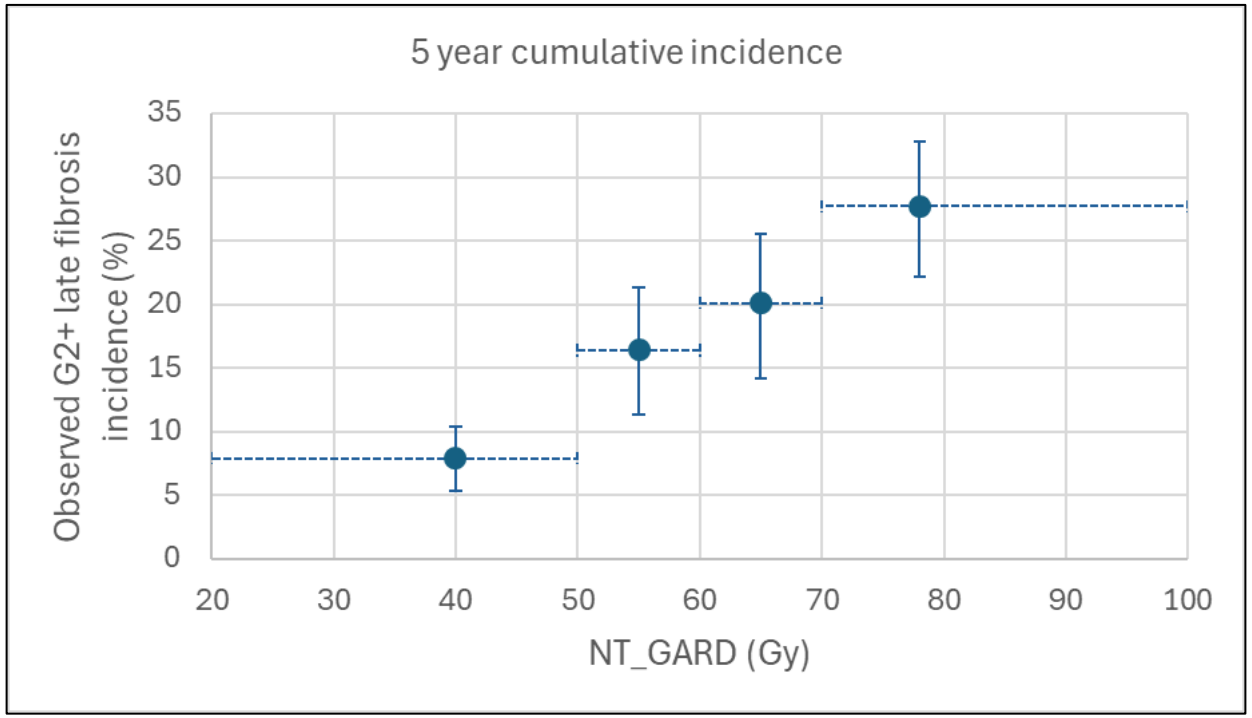
# EQD2MaxD vs NT_GARD




Distribution of normal tissue genetically-adjusted dose (NT_GARD) compared with the maximum physical dose to the WB (EQD2MaxD). The black line indicates the identity line (y = x), while red dots are patients with CTCAE grade≥2 fibrosis (13%).

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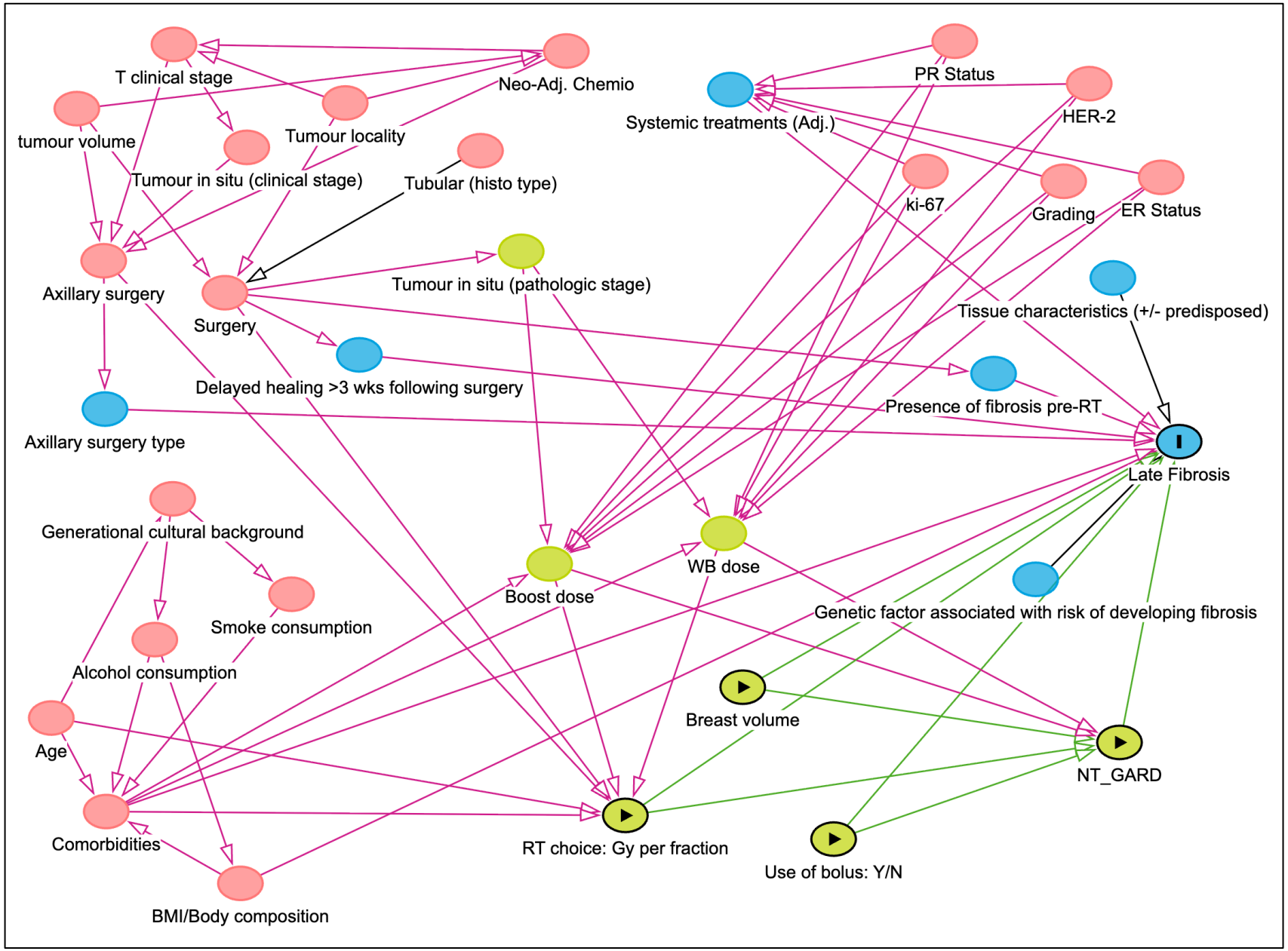
# The causal framework for late fibrosis




**Optimal adjustment set**:

- Age
- Axillary surgery type
- Presence of comorbidities
- Delayed healing >3 weeks after surgery
- Presence of fibrosis pre-RT
- Use of systemic treatments (Adj.)

A bootstrapped multivariable Cox model highlighted NT_GARD significantly associated with the risk of late fibrosis, with an HR=1.037 per 1 genetically adjusted Gy ($IC_{95\%} = (1.027\,, 1.047)$).

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# Conclusions

- By explicitly incorporating genetic susceptibility into dose modelling, NT_GARD provides a biologically grounded, patient-specific measure of effective radiation dose.

- The causal-derived analysis confirmed the association between the NT_GARD and the risk of developing late fibrosis.

**Thank you for the attention!**

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