



Original Research

# Accuracy of the online prognostication tools PREDICT and Adjuvant! for early-stage breast cancer patients younger than 50 years



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**Abstract Importance:** Online prognostication tools such as PREDICT and Adjuvant! are increasingly used in clinical practice by oncologists to inform patients and guide treatment decisions about adjuvant systemic therapy. However, their validity for young breast cancer patients is debated.

**Objective:** To assess first, the prognostic accuracy of PREDICT's and Adjuvant! 10-year all-cause mortality, and second, its breast cancer-specific mortality estimates, in a large cohort of breast cancer patients diagnosed <50 years.

**Design:** Hospital-based cohort.

**Setting:** General and cancer hospitals.

**Participants:** A consecutive series of 2710 patients without a prior history of cancer, diagnosed between 1990 and 2000 with unilateral stage I–III breast cancer aged <50 years.

**Main outcome measures:** Calibration and discriminatory accuracy, measured with C-statistics, of estimated 10-year all-cause and breast cancer-specific mortality.

**Results:** Overall, PREDICT's calibration for all-cause mortality was good (predicted versus observed)  $\text{mean}_{\text{difference}} = -1.1\%$  (95%CI:  $-3.2\%$ – $-0.9\%$ ;  $P = 0.28$ ). PREDICT tended to underestimate all-cause mortality in good prognosis subgroups (range  $\text{mean}_{\text{difference}} = -2.9\%$  to  $-4.8\%$ ), overestimated all-cause mortality in poor prognosis subgroups (range  $\text{mean}_{\text{difference}} = 2.6\%$ – $9.4\%$ ) and underestimated survival in patients < 35 by  $-6.6\%$ . Overall, PREDICT overestimated breast cancer-specific mortality by  $3.2\%$  (95%CI:  $0.8\%$ – $5.6\%$ ;  $P = 0.007$ ); and also overestimated it seemingly indiscriminately in numerous subgroups (range  $\text{mean}_{\text{difference}} = 3.2\%$ – $14.1\%$ ). Calibration was poor in the cohort of patients with the lowest and those with the highest mortality probabilities. Discriminatory accuracy was moderate-to-good for all-cause mortality in PREDICT (0.71 [95%CI: 0.68 to 0.73]), and the results were similar for breast cancer-specific mortality. Adjuvant!'s calibration and discriminatory accuracy for both all-cause and breast cancer-specific mortality were in line with PREDICT's findings.

**Conclusions:** Although imprecise at the extremes, PREDICT's estimates of 10-year all-cause mortality seem reasonably sound for breast cancer patients <50 years; Adjuvant! findings were similar. Prognostication tools should be used with caution due to the intrinsic variability of their estimates, and because the threshold to discuss adjuvant systemic treatment is low. Thus, seemingly insignificant mortality overestimations or underestimations of a few percentages can significantly impact treatment decision-making.

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## 1. Introduction

In 2015, a total of 14,449 women were diagnosed with invasive breast cancer in The Netherlands, of which 20% were younger than 50 years at diagnosis [1]. Available evidence strongly suggests that breast tumours are more aggressive in young (especially those <40 years) than in post-menopausal women [2–5]. This is partly due to the over-representation of aggressive biological features (e.g. oestrogen receptor [ER] negative, grade 3) in young patients [2–5]. Yet, even after controlling for known biological factors indicative of tumour aggressiveness, young age in itself remains an independent predictor of poor cancer-specific survival and strongly correlates with the risks of local recurrence and contralateral breast cancer [4,6,7]. Therefore, pending better molecular characterisation of tumours in young women, young age itself and classical tumour characteristics, remain important prognosticators.

Accurate quantification of long-term disease outcome and potential adjuvant systemic treatment benefit could help oncologists and patients in tailoring treatment

decisions, also considering the potential side-effects of and possibly reduced quality of life during/after systemic therapy. Furthermore, adequately informing patients about such probabilities as well as the side-effects of treatment could empower them to choose the treatment option that best fits their preferences. Adjuvant! [8,9] and PREDICT [10,11] are online prognostication tools, that provide personalised 10-year all-cause and/or breast cancer-specific mortality estimates for the adjuvant treatment setting. Both tools base their predictions on patient (e.g. age) and tumour (e.g. size, nodal status, ER-status and grade) characteristics.

Clinicians reported common use of Adjuvant! during consultations with patients [12,13]; PREDICT's average user access is 10,000 per month as per February 2016, and currently probably higher as Adjuvant! has been offline for some time. Further, the Dutch national breast cancer guideline based its treatment recommendations on Adjuvant!'s estimates and leading British and American guidelines endorsed Adjuvant!'s use to quantify prognosis [14–16]. Adjuvant! and PREDICT have mainly been externally validated in North American and European

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