Tailored to fit: balancing over- and undertreatment in early-stage triple-negative breast cancer patients

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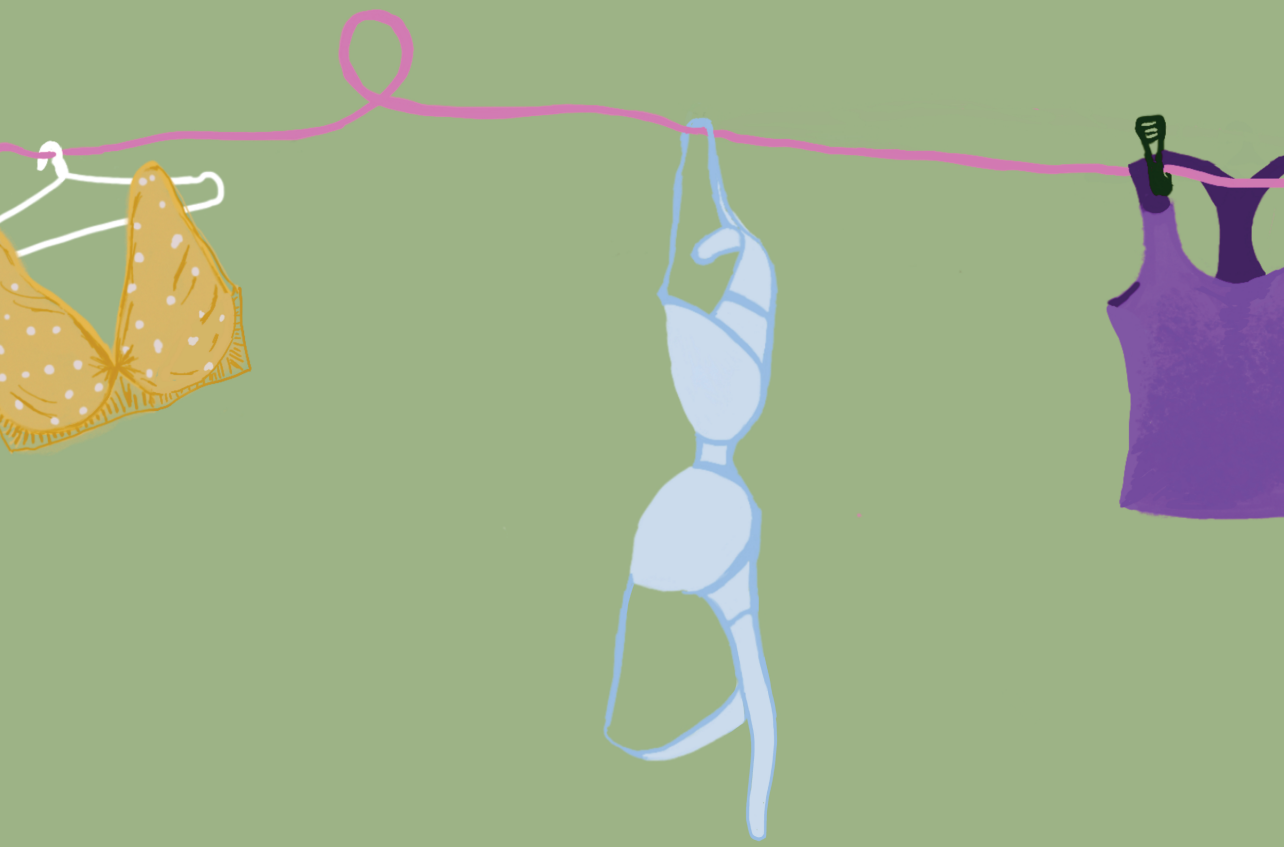

CHAPTER 7

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Nederlandse samenvatting
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SUMMARY

Triple-negative breast cancer (TNBC) accounts for 10–20% of breast cancer cases and is characterized by its aggressive nature. Due to the absence of estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2, (neo)adjuvant chemotherapy has remained the sole systemic treatment for early-stage TNBC patients until the recent introduction of PARP inhibitor and PD-1/PDL-1 inhibitor for the high-risk group. However, chemotherapy remains the primary option for most TNBC patients, especially for young patients. Studies have shown potential overtreatment in node-negative TNBC patients. This overtreatment suggests an unmet need for a better risk classification in early-stage TNBC patients, and immune biomarkers such as stromal tumor infiltrating lymphocytes (sTILs), and genetic biomarkers such as germline *BRCA1* mutation can potentially aid in identifying low-risk patients. However, the true prognostic values of these biomarkers have remained unclear due to the scarcity of data from chemotherapy-naïve TNBC patients, especially from young patients (**Chapter 1**). This thesis aimed to refine risk classification in early-stage TNBC using TILs and *BRCA1* related biomarkers, and to identify high-risk patients who need chemotherapy and low-risk patients who may avoid it or de-escalate it. We first validated the PREDICT breast cancer prognostic model in young, early-stage breast cancer patients who did not receive systemic treatment (**Chapter 2**). Then we assessed genomic and immune biomarkers in young, early-stage TNBC patients (**Chapters 3 and 4**), and lastly, we updated the PREDICT model by incorporating sTILs to enhance treatment decision-making for early-stage TNBC patients across all age groups.

In **Chapter 2**, we externally validated the PREDICT breast cancer prognostic model using the PARADIGM cohort, which consists of young, systemic treatment-naïve breast cancer patients with node-negative disease. This validation is of high importance because decisions regarding chemotherapy rely on accurate prognostication prior to any systemic treatment, while the model validation in chemotherapy-naive patients had not been conducted before. Our findings showed that the model underestimated all-cause mortality in this cohort. Furthermore, it displayed only a 55% probability of accurately distinguishing between patients who would survive for 10 years and those who would not. We demonstrated that the model did not offer any additional clinical utility compared to the strategy of administering chemotherapy to all patients with ER-negative breast cancers. This limited clinical utility emphasizes the need for updating the PREDICT model with prognostic factors relevant for young, systemic treatment-naïve patients, particularly those with ER-negative and TNBCs.

In **Chapter 3**, we investigated the prognostic value of sTILs in young, node-negative, chemotherapy-naïve TNBC patients. We showed that a per 10% increase in sTILs was associated with a 19% reduction in all-cause mortality in these patients after adjusting for tumor

characteristics and local treatment. This finding is consistent with studies conducted in other TNBC populations across varying ages and treatment conditions, reinforcing the independent prognostic value of sTILs in TNBC patients. Additionally, we demonstrated that patients with stage II tumors and high sTILs had better survival outcomes than those with stage IB tumors and low sTILs, suggesting sTILs may refine risk classification beyond tumor size in young TNBC patients.

In **Chapter 4**, we examined *BRCA1*-related biomarkers in the same patient population, grouping patients by germline *BRCA1* mutation, somatic *BRCA1* mutation, and *BRCA1* promoter methylation. We found that germline *BRCA1* mutations were associated with poorer long-term survival and higher incidence of second primary tumors compared to other *BRCA1* statuses in these young, chemotherapy-naive TNBC patients. The poor overall survival in germline *BRCA1* mutation carriers was partially mediated by the high incidence of second primary tumors. Furthermore, we found that sTILs maintained their prognostic value across *BRCA1* subgroups and had an even stronger association with overall survival in patients with *BRCA1* promoter methylation, suggesting potential differences in sTILs composition by *BRCA1* status. Using *BRCA1* status and sTILs, we identified a low-risk group of patients characterized by having ≥50% sTILs and tumor *BRCA1* promoter methylation. These patients showed a 97% 15-year overall survival without receiving chemotherapy.

To translate these findings into clinical applications, we focused on integrating sTILs into the PREDICT model (version 2.3) for TNBC patients in **Chapter 5**. We collected data from two pooled cohorts: one comprising chemotherapy-naïve TNBC patients and the other including patients treated with anthracycline-based and/or taxane-based chemotherapy. The updated model, PREDICT_sTILs, underwent rigorous internal validation using leave-one-region-out cross-validation, and showed good model performance in these patients. Decision curve analysis showed improved clinical utility of PREDICT_sTILs compared to the original PREDICT model and the chemotherapy-to-all strategy in most risk thresholds. These findings suggest the potential of PREDICT_sTILs in personalizing chemotherapy decisions, providing a balance between treatment efficacy and minimizing overtreatment in TNBC patients. Though promising, external validation of PREDICT_sTILs by independent research groups is still needed before its clinical application, especially in patients with different ethnicities or breast cancer genetic predisposition.

In conclusion, we evaluated the true prognostic values of sTILs, germline *BRCA1* mutations, and *BRCA1* promoter methylation in young, early-stage TNBC patients. Additionally, we highlighted the limitations of using the PREDICT model to inform chemotherapy decisions in young, node-negative breast cancer patients, particularly those with ER-negative and TNBC. To enhance chemotherapy decision-making for TNBC patients, we incorporated sTILs into

the PREDICT model. The updated model, referred to as PREDICT_sTILs, demonstrated significant potential for personalized chemotherapy decision-making in early-stage TNBC patients. Future updates to PREDICT_sTILs may consider including germline *BRCA1* mutations as well as additional treatment options, such as PD-1/PD-L1 inhibitors. Most importantly, external validation of PREDICT_sTILs across diverse cohorts is essential before it is adopted in clinical practice.