



Original Research

# Recurrence dynamics of breast cancer according to baseline body mass index<sup>☆</sup>



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## KEYWORDS

Breast cancer;  
Body mass index;  
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**Abstract Background:** In cancer follow-up, in addition to the evaluation of survival probabilities, there is a fundamental need of assessing recurrence dynamics for optimal disease management. Although the time-dependent effect of the oestrogen receptor (ER) status of the tumour has already been described, so far no factor has proven to disentangle the multi-peak behaviour observed for breast cancer recurrences. Here, we aimed at investigating whether adiposity at diagnosis, reflected by increased patient’s body mass index (BMI), could

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be associated with breast cancer recurrence patterns over time after primary cancer therapy.

**Methods:** We retrieved BMI from 734 of 777 patients with node-positive breast cancer from a phase III randomised clinical trial, which compared different chemotherapy regimens and had a median follow-up of 15.4 years. Cumulative incidence estimation as well as piecewise exponential models were carried out to estimate the distant recurrence dynamics, in all patients, as well as in subgroups based on the ER status, with the ER-positive group being further split according to the menopausal status.

**Results:** In patients with ER-negative breast cancer, time-dependent analyses revealed that the hazard of late relapses could mainly be attributed to the overweight and obese patients. Within the subgroup of premenopausal patients with ER-positive tumours, obesity was associated with an early high narrow peak of distant recurrences followed by another main peak after 5 years of follow-up. The risk for overweight patients was intermediate between obese and normal-weight patients. In the postmenopausal subgroup of patients with ER-positive tumours, the distant recurrence rate was significantly more elevated in the overweight patients compared to the other BMI categories, and a second late peak of recurrences was also observed for the obese patients.

**Conclusion:** These results demonstrate that the patient's BMI at diagnosis is associated with cancer recurrence dynamics. Patient adiposity should therefore be central to the exploration of late adjuvant treatment modalities.

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## 1. Background

According to the latest estimates, 39% of women worldwide are either overweight or obese [1]. This percentage is country-dependent and reaches, for example, 63% in the United States of America [1]. Besides being an important risk factor for cardiovascular and kidney diseases as well as diabetes, elevated body mass index (BMI) has been recognised as a risk factor for developing breast cancer, especially oestrogen receptor (ER)-positive breast cancer in postmenopausal women [2]. Many studies have investigated the association between baseline BMI and various survival end-points, using either institutional cohorts or data from randomised clinical trials (reviewed by Jiralerspong and Goodwin [3]). Although most of these studies have reported an adverse association between obesity and survival, discrepant results have been noticed, which may be explained by the heterogeneity of the studies regarding the patient characteristics, the definitions and categorisation of obesity, the considered end-points, the length of the follow-up, the administered treatment and the subgroup analyses, among others. Although it has been suggested that the deleterious association between obesity and survival might be due to the reduced chemotherapy dose administered in obese patients, with an arbitrary cap at 2 m<sup>2</sup> for fear of increased toxicity, this association was still observed in trials without such a cap [4].

Following an early report [5], several studies have established the multi-peak behaviour of breast cancer recurrences over time [6–8], which is more pronounced when considering patients with 'aggressive' features such as axillary lymph node involvement or a large tumour

size. The occurrence of these consistent recurrence peaks over time supports the concept that dormant tumour foci are recruited to grow after surgical removal of the primary tumour [9]. Of interest, these peaks seem to be driven mainly by distant metastases and do not differ according to the site of distant metastasis [10]. It has repeatedly been demonstrated that the ER content of the tumour does influence the pattern of recurrence, with the ER-negative tumours presenting a higher rate in the first 5 years of follow-up, the hazard curves of ER-negative and -positive tumours crossing at 3–4 years and the ER-negative tumours presenting a lower rate of recurrence after 5 years [11–16].

Here, we hypothesised that patient adiposity at baseline, reflected by increased baseline BMI, might be associated with the escape from breast cancer dormancy and disease progression after primary cancer therapy and might therefore be an additional factor related to the recurrence dynamics. Specifically, we aim to study the hazard patterns over time in an established clinical trial case series with very long follow-up [17]. First, we present the associations between baseline BMI and the standard clinico-pathological parameters; second, the potential prognostic value of BMI using univariable and multivariable survival regression analyses and finally, our main objective, the hazard function patterns over time according to BMI.

## 2. Patients and methods

### 2.1. Patient population

For this study, we considered the patients from the Belgian phase III study, which compared higher dose

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