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Original article

Propensity score to evaluate prognosis in pregnancy-associated breast cancer: Analysis from a French cancer network

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ABSTRACT

Purpose: To compare the prognosis of pregnancy associated breast cancer occurring during pregnancy (BCP) to non-pregnancy associated breast cancers (non-BCP) in young women managed at a national expert center.
Methods: Retrospective cohort study of a prospective database using propensity score matching (PSM) analysis with known prognostic factors.
Results: We analyzed data of 49 patients with BCP and 104 with non-BCP diagnosed between 2002 and 2017 at Tenon University Hospital (Paris, France). The BCP tumors were often locally advanced (lymph node metastases in 59%), of high grade (55%) and highly proliferative (67% with Ki67 $\geq$ 20%). After PSM, breast cancer-free survival ($p = 0.45$) and breast cancer specific survival ($p = 0.81$) were similar in the two groups. The recurrence rate was 12% vs 18% ($p = 0.45$) and the death rate was 6% vs 8% ($p = 0.74$) for the BCP and non-BCP groups, respectively. No difference in recurrence type was observed between the groups ($p = 0.60$).
Conclusions: After PSM for known prognostic factors, the prognosis of BCP patients did not differ from that of young patients with non-BCP.

1. Introduction

The prevalence of pregnancy associated breast cancer, commonly defined as breast cancer diagnosed during pregnancy or during the year following delivery, is relatively low (1/1000–1500). However, it constitutes a major medical challenge related to the impact of treatment on both maternal and fetal outcome [1,2]. In view of the clinical complexity of cancers occurring during pregnancy, a national network – the CALG (Cancer Associé à La Grossesse) network – was created in France in 2008.

Although it is now recognized that the tumor stage, histological characteristics as well as surgical and medical management differ between breast cancer occurring during pregnancy and breast cancer occurring during the post-partum period [3–5], national and international guidelines recommend that pregnancy associated breast cancer treatment should be as similar as possible to that in non-pregnant patients with breast cancer [6].

Furthermore, the maternal prognosis of pregnancy associated breast cancer, and especially the impact of pregnancy, is highly debated. Some authors report that pregnancy itself negatively

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influences the prognosis by specific involvement of the pro-inflammatory micro-environment of mammary gland, while others suggest that the prognosis is similar in pregnant and non-pregnant patients [5,7,8]. So far, few studies have compared breast cancer in young patients with and without pregnancy [5,9]. Those that have done so have failed to find a difference in recurrence or survival between the two populations. This could be linked to various confounding factors such as the inclusion in the pregnancy associated breast cancer population of both true breast cancer pregnancy (BCP) (occurring during pregnancy) and breast cancer occurring in the post-partum period as well as matching failure to match the populations based on epidemiological, histological and tumor stage criteria.

The aims of the current study were therefore to compare the prognosis (recurrence rate, disease-free and overall survivals) of patients with true BCP diagnosed during pregnancy to non-pregnant patients with breast cancer using a propensity score matching (PSM) analysis.

2. Material and methods

2.1. Study population

Data of women with histologically proven invasive breast carcinoma aged under 46 years old at the time of diagnosis, between January 2002 and April 2017, were retrospectively collected from the prospective database of Tenon University Hospital (Paris, France) participating to the CALG cancer network. The age of 46 was set as the threshold as it corresponded to the oldest patient with BCP in our cohort. We included all women with BCP diagnosed during pregnancy (the BCP group) and women with breast cancer that was not associated with pregnancy (the non-BCP group). Patients diagnosed with breast cancer during the year following delivery (post-partum BCP) were excluded from the study.

For all the patients, epidemiological data (age at diagnosis, genetic mutation, familial or personal history of cancer), histological and immunohistochemical data (histological grade according to Ellis and Easton, hormonal-receptor status (estrogen receptors (ER) and progesterone receptors (PR)), HER2 overexpression, Ki67 expression) were recorded. The histological data corresponded to surgical specimens, except when a neoadjuvant chemotherapy was performed in which case biopsy data and initial imaging data were used. For patients undergoing neoadjuvant chemotherapy, lymph node status was determined on the result of axillary lymph node cytology before chemotherapy and on analysis of a surgical specimen using the Sataloff criteria [10].

ER and/or PR status was considered to be positive when $\geq$10%. In case of an intermediary HER2 expression (score 2), a fluorescent *in situ* hybridization test (FISH) was performed. Tumor was considered proliferative when Ki67 was $\geq$15% but an analysis with a Ki67 $\geq$ 20%, the usual cut-off used in France. In both groups, patients received the same chemotherapy (anthracyclines (adriamycin or epirubicine), taxanes and cyclophosphamide), trastuzumab in case of HER2 overexpression, tamoxifen as endocrine therapy in case of positive hormonal receptors. However, during pregnancy, no patient received tamoxifene neither trastuzumab.

2.2. Statistical analysis

2.2.1. Propensity score (PS) and matching procedures

The population was divided into two groups – BCP and non-BCP – and compared in terms of demographics and treatment characteristics, before PSM. A PS was then generated using a logistic regression model as described by Rosenbaum and Rubin based on the patients' demographics and histological findings [11,12]. Covariates were then included in the model to optimize the matching procedure by reducing bias related to parameters known to negatively impact survival and recurrent disease outcome from previous studies. The following covariates were included: age at diagnosis ($p = 0.03$), tumor size ($p = 0.05$) and HER2 overexpression ($p = 0.07$) for the BCP group [5].

A PS was then assigned to each patient to determine the conditional probability of being BCP or non-BCP (control). The area under the receiver operating characteristic (ROC) curve [13] for this model was 0.70 (0.68–0.72). Each woman of the BCP group was matched (a 1:1 match) to a corresponding woman in the non-BCP group using an optimal matching algorithm by randomly selecting for each pair with the closest PS. We applied a caliper matching approach to avoid bad matches (i.e., women whose PS differed by more than the defined caliper width).

2.2.2. Definition and classification of recurrence

Recurrent disease was assessed by physical examination, histological findings, clinical follow-up and imaging. Breast cancer-free survival was defined as time from diagnosis to breast cancer recurrence and was censored at the date of last the follow-up or at the date of death without recurrence. Breast cancer specific survival was defined as time from diagnosis to breast cancer-related death. Recurrence events were defined as: i) local if recurrence was ipsilateral; ii) regional if ipsilateral axillary recurrence, iii) distant if metastasis to bone, liver, lung, brain or peritoneum, and for contralateral axillary recurrence.

2.2.3. Other statistical analyses

Statistical analysis was based on the Student's *t*-test or ANOVA test as appropriate for continuous variables, and the Chi-square test or Fisher's exact test as appropriate for categorical variables. Values of $p < 0.05$ were considered to denote significant differences.

The Kaplan–Meier method was used to estimate the cumulative rates (CRs), and comparisons of CRs were made using the log-rank test. Data were analyzed using R 3.0.1 software, available online.

3. Results

3.1. Characteristics of the population

The data of 339 women eligible for analysis were initially extracted from the database of Tenon University Hospital and the CALG network. Fifty-four patients were excluded from analysis because the breast cancer was diagnosed during the postpartum period. The remaining 285 women, 50 with BCP and 235 with non-BCP, comprised the study population before PSM.

The epidemiological, histological and treatment characteristics of the population before and after PSM are summarized in Tables 1 and 2.

Before PSM, a higher median age at diagnosis (37 (33–40) vs 35 (31–38), $p = 0.03$), and a trend for a greater tumor size ($p = 0.05$) and higher HER2 overexpression rate (23% vs 12%, $p = 0.07$) was observed in the non-BCP compared to the BCP group. There was also a trend for a higher rate of hormonal receptors (71% vs 60%, $p = 0.11$) and multifocal tumors (28% vs 16%, $p = 0.08$) in the non-BCP compared to the BCP group. In the BCP group, most of the tumors were locally advanced (60% N+), of high grade (56% grade 3 tumor) and proliferative (66% Ki67 $\geq$ 20%). Patients in the non-BCP group were more likely to have undergone radical breast surgery (54% vs 46%, $p = 0.007$), with a trend for a higher rate of sentinel node procedures (39% vs 26%, $p = 0.08$) and endocrine therapy (72% vs 58%, $p = 0.05$) compared to the BCP group. Chemotherapy was more frequent in the BCP group than in the non-BCP group (42%