Survival analysis of pregnancy-associated breast cancer: multiparous women might have better outcomes

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Abstract
Purpose: Pregnancy-associated breast cancer (PABC) is an aggressive disease and since China began to encourage childbearing in 2015, the incidence of PABC has increased. The study was to investigate the characteristics and survival rates of PABC patients.

Methods: Patients with PABC who underwent surgery at Fudan University, Shanghai Cancer Center, from 2005 to 2018 were enrolled. First, the study divided the population into two groups: first-pregnancy group and non-first pregnancy group. Second, patients were categorized as those having breast cancer during pregnancy with/without an abortion or during the lactation period.

Results: Overall, 203 patients were recruited. Since 2016, 63.9% patients were diagnosed with PABC during their second or third pregnancy, while at that time in Shanghai, only 25% of newborns were non-first births. Luminal B accounted for the highest proportion (38.4%), followed by triple-negative breast cancer (30.0%). Compared with the non-first pregnancy group, the first-pregnancy group preferred to delay treatment until the fetus was born (time from initial symptoms to treatment: 6.20 vs. 4.67 m, P=0.106). The patients in the first pregnancy group were presented with 57.0% of HR negative tumors and 26.6% of HER-2 positive tumors, while the HR negative tumors accounted for 47.6% (P=0.281) and the proportion of HER-2 positive tumors was 36.3% (P=0.108) in the non-first pregnancy group. The 3-year disease-free survival rate of the first-pregnancy group was 78.4%, and that of the non-first pregnancy group was 83.7% (P=0.325).

Conclusions: Our study proves that the proportion of PABC developed during the second or third pregnancy of women was extremely large relative to the newborn populations. Patients in the first-pregnancy group tended to be presented with less aggressive tumor pathological characteristics but a worse survival outcome than those in the non-first pregnancy group.

Background
Breast cancer is the most common cancer in women worldwide [1]. In a woman’s life, pregnancy and breastfeeding are important physiological activities, and when they collide with breast cancer, management becomes challenging. The concurrence of cancer and pregnancy is rare; however, breast cancer remains the most frequently diagnosed cancer during this period [2]. In the US, it is
estimated that approximately 3500 cases of newly diagnosed cancer occur in pregnant women every year, which is equivalent to one in every 1000 pregnancies have cancers [3]. The incidence of breast cancer related to pregnancy is approximately 0.2%–3.8% [4]. In western countries, the occurrence of breast cancer is estimated to range from 1 in 3000 to 1 in 10,000 pregnancies [5]. Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or within one year after pregnancy [6]. In October 2015, to actively address the aging of the population, China abolished the restriction in which a couple can have only one child. Being able to have a second child means longer periods of pregnancy and breastfeeding and an older age at pregnancy, thereby increasing the risk of developing PABC than in women who only have one child [7]. Since then, at our clinical center, we have observed that the growth rate of PABC and sporadic breast cancer has been disproportionate. The growth rate of PABC, especially that in non-first-pregnancy women, has increased in recent years, which attracted our attention. Unfortunately, a thorough understanding of this problem is lacking, and further investigation based on the Chinese population is urgently needed. Therefore, we enrolled 203 women at Fudan University, Shanghai Cancer Center (FUSCC), to study the impact of parity and lactation on the clinical characteristics and prognosis of PABC.

Patients And Methods

Eligible Participants

In this retrospective study, we reviewed the medical records of patients who underwent surgery from January 2005 to December 2018 at the Department of Breast Surgery, FUSCC. Eligible patients were women who had local or regional invasive unilateral breast cancer, with their first symptoms occurring during pregnancy or lactation. The lactation period usually refers to the year after childbirth. Patients diagnosed with stage IV breast cancer who had recurrence or distant metastasis, bilateral breast cancer, benign lesions including fibroma, mastitis, breast hyperplasia and breast cysts, and non-epithelial-derived tumors including sarcomas and phylloides tumors were excluded from our study.

Study Design
This research was conducted with two classification schemes to study the clinical characteristics and prognosis of PABC. First, the population was divided into first-pregnancy and non-first-pregnancy groups. First-pregnancy patients were defined as women with breast cancer during the pregnancy or lactation period of their first child, while non-first-pregnancy patients were defined as women with PABC during the pregnancy or lactation period of their second, third or more child. Second, the population was redivided into the breast cancer during pregnancy group and breast cancer during the lactation period group. Breast cancer during pregnancy consisted of two subgroups: the abortion group, which included women who chose to terminate their pregnancies and receive immediate treatment (patients in the early stage of pregnancy were strongly recommended), and the non-abortion group, which included women who preferred to delay treatment until the fetus was born.

All patients diagnosed with PABC between January 2005 and December 2018 were enrolled in this study. To analyze the clinicopathological characteristics of PABC, study variables included the age of the patients, the gestational age at the appearance of the first symptoms (months), the family history of breast cancer, the surgery type and other treatments (adjuvant chemotherapy, neoadjuvant chemotherapy, radiotherapy, endocrine therapy and targeted therapy), the clinical tumor size and pathological lymph node stage, vascular invasion, the pathological type and histological grade of the tumor, the expression of hormone receptor (HR), the expression of human epidermal growth factor receptor-2 (HER-2), and the rate of Ki-67 positivity.

In the survival analysis, patients diagnosed with PABC after 2016 were excluded to ensure a follow-up time of more than 3 years. Disease-free survival (DFS) was defined as the time between the first date of diagnosis to any locoregional recurrence, including ipsilateral breast, local/regional lymph nodes of the disease, any contralateral breast cancer, any distant metastasis of the disease, or any secondary malignancy, whichever occurred first [8,9].

**Statistical Analysis**

Chi-square tests were used to compare the histopathological characteristics of the tumors and clinical features of the patients among the different subgroups. The Kaplan-Meier methods were used to perform the survival analysis. All tests were two-sided, and a P-value of less than 0.05 was considered
statistically significant. All statistical analyses were performed using SPSS statistical software version 25.0 package (IBM Corporation, Armonk, NY, USA).

Results

Tumor Characteristics

A total of 203 patients were diagnosed with PABC from 2005 to 2018 in FUSCC, and the median age of the study population was 33 years (range, 23 years to 46 years). Among the 203 patients diagnosed with PABC, 79 (38.9%) women developed breast cancer during their first pregnancies (first-pregnancy group), and 124 (61.1%) women developed breast cancer during their second or third pregnancies (non-first-pregnancy group). Since 2016, 63.9% of patients with PABC were diagnosed during their second or third pregnancies, while at that time in Shanghai, only 25% of newborns were non-first births (according to the China Health and Wellness Development Statistics). The mean age of the first-pregnancy group was 30.8 years, while that of the non-first-pregnancy group was 35.3 years. Table 1 shows the distribution of tumor characteristics according to first/non-first-pregnancy subgroup. The first-pregnancy group was younger than the non-first-pregnancy group (P = 0.000). The proportion of HR-positive tumors in the first-pregnancy group was 57.0%, and the proportion in the non-first-pregnancy group was 47.6% (P = 0.281). In the first-pregnancy group, the proportion of HER–2-positive tumors was 26.6%, while that in the non-first-pregnancy group was 36.3% (P = 0.108). Regarding the second classification, the tumor characteristics of the three subgroups are demonstrated in Table S1 (Additional file 1). A total of 89 women were diagnosed with breast cancer during pregnancy. Among them, 66 pregnant women (74.2%) gave birth to healthy surviving fetuses by vaginal delivery or cesarean section, and the other 23 pregnant women (25.8%) had spontaneous or elective abortions. A total of 114 (56.2%) of the women developed breast cancer during the lactation period, and the mean ages of the three subgroups were 34.4, 33.7 and 33.3 years, respectively. Compared with the pregnancy (non-abortion) group, the pregnancy (abortion) group tended to have smaller tumor sizes (P = 0.544), higher HR positivity rates (P = 0.319), lower HER–2 positivity rates (P = 0.527) and lower Ki–67 expression (P = 0.110).

The proportions of breast cancer subtypes among the total population are presented in Figure 1A,
demonstrating that luminal B accounted for the highest proportion (38.4%) among the total population, followed by triple-negative breast cancer (TNBC, 30.0%). The trend was similar in the first-pregnancy group (Figure 1B) and the non-first-pregnancy group (Figure 1C). Figure 2 shows the distribution of the breast cancer subtypes classified by pregnancy or lactation. Notably, the proportion of TNBC in the pregnancy (non-abortion) group (30.3%, Figure 2A) and the lactation group (32.5%, Figure 2B) was much higher than that in the pregnancy (abortion) group (17.4%, Figure 2C).

**Treatments**

Compared with the non-first-pregnancy group, the first-pregnancy group preferred to delay treatment until the fetus was born (proportion of non-abortion cases: 85.7% vs. 68.9%, P = 0.092). The times from initial symptoms to initiation of treatment, such as surgery or neoadjuvant chemotherapy, were 6.20 months and 4.67 months for the first-pregnancy and non-first-pregnancy groups (P = 0.106), respectively.

A total of 84 patients (41.4%) received neoadjuvant chemotherapy, and 18 (21.4%) achieved pathologic complete response (pCR). The proportions of neoadjuvant chemotherapy in the first-pregnancy and non-first-pregnancy groups were 46.8% and 37.9% (P = 0.208), respectively (Table 1). The proportions in the pregnancy (non-abortion) group and the pregnancy (abortion) group were 43.9% and 39.1% (P = 0.688), respectively (Table S1). All patients were treated with surgery, and the main surgical procedure was mastectomy with sentinel lymph node biopsy/axillary lymph node dissection. A total of 196 women (96.6%) received adjuvant/neoadjuvant chemotherapy, and anthracycline combined taxane chemotherapy (53.5%) was the most commonly used regimen. The general chemotherapy regimens were CEF (cyclophosphamide, epirubicin sequential fluorouracil), EC-T (epirubicin, cyclophosphamide sequential docetaxel), FEC-T (epirubicin, cyclophosphamide, fluorouracil sequential docetaxel) and EC-P (epirubicin, cyclophosphamide sequential paclitaxel).

Although trastuzumab was recommended for all patients with HER-2-overexpressing tumors, not all patients could afford the high cost. The proportions of HER-2-positive patients receiving targeted therapy with trastuzumab were 67.6%, 71.4%, and 72.7% in the lactation group, pregnancy (abortion) group, and pregnancy (non-abortion) group, respectively (Table S1).
Survival Analysis

For all patients diagnosed with PABC before 2016, the median follow-up period was 59.0 months (range, 2 months to 144 months). The 3-year DFS rates for the first-pregnancy group and non-first-pregnancy group were 78.4% and 83.7%, respectively. The survival curve showed the trend of a worse prognosis in the first-pregnancy group compared with the non-first-pregnancy group (Figure 3, P = 0.325). Regarding the other categorization, the 3-year DFS rates for the pregnancy (abortion) group, pregnancy (non-abortion) group and lactation group were 86.2%, 74.4% and 85.4%, respectively. Figure 4 shows that the lactation group and the pregnancy (abortion) group tended to have better survival than the pregnancy (non-abortion) group (P = 0.278).

Discussion

Although PABC is still relatively rare, with an incidence of only 0.2%–3.8% [9], the number of cases is likely to increase because it is common to delay childbearing in today’s society [10]. The older age at pregnancy usually indicates a higher risk of developing cancer [11]. Once a PABC diagnosis is made, challenges lie not only in deciding on the choice of the mother’s treatment and the survival of the fetus but also in addressing a series of complex problems, such as distant metastasis and preterm birth complications [5].

In this present study, we reviewed 25 studies in the past 20 years to gain a deeper understanding of PABC (Table 2). Almost all existing studies regarded PABC as the experimental group and non-PABC as the control group. PABC was defined as breast cancer occurring during pregnancy or within 1 year after pregnancy in 16 studies, while it was defined as breast cancer diagnosed during pregnancy or within 2 years postpartum in 8 studies. The survival rates for PABC compared to those for non-PABC were conflicting. Eight studies [12–17,7,18] showed no difference in survival between PABC and non-PABC after correcting for prognostic factors including age, tumor size, and lymph node status, while 12 studies [19–30] demonstrated a worse prognosis for PABC after excluding these factors. Five studies [31–35] classified PABC into antepartum and postpartum breast cancer, three studies showed that the prognosis of PABC occurring postpartum was worse than that of PABC during gestation, one study concluded that the prognosis of PABC occurring in the antepartum period was worse, and one
study indicated that PABC occurring postpartum had a worse survival rate than non-PABC. The reasons for the poor prognosis of PABC may include several factors. First, the physical changes in the mammary gland, including increased cell turnover and glandular tissue during pregnancy, make the diagnosis of PABC difficult [36]. In addition, fluctuations in hormone levels during pregnancy may promote tumor progression and breast involution; moreover, tissue remodeling of the breasts after breastfeeding may promote tumorigenesis [37,38].

The first part of the classification in our study was based on first-pregnancy and non-first-pregnancy status to explore the effect of parity on PABC. The frequency of PABC in women with more than one pregnancy has increased as more women have chosen to have a second child since China abolished the restriction in which one couple could only have one child. Our study proves that the proportion of PABC that developed during the second or third pregnancies of women was extremely high relative to the proportion of newborns. Our study also showed that compared with the non-first-pregnancy group, the first-pregnancy group presented with less aggressive tumors, which were more likely to be smaller in size, show HR positivity, exhibit lower Ki–67 expression and have a lower histological grade, which were related to a better prognosis. However, our survival analysis showed the opposite result: the PABC patients in the first-pregnancy group were more likely to have a worse outcome. There are several possible reasons for this result. First, our data showed that a woman in her first pregnancy was more likely to delay treatment until the fetus was born. Delayed treatment may be a vital factor for a poor prognosis. Second, there may be a protective effect from the previous pregnancy on women with PABC who have had more than one child [39]. In addition, the women in the first-pregnancy group were younger than those in the non-first-pregnancy group. Studies have indicated that breast cancer in young women is an invasive disease with a poor prognosis, and age may be a factor that is independent of pregnancy, resulting in a poorer survival rate for the younger first-pregnancy group [40–42]. In addition, previous studies have shown that a family history of breast cancer can increase the risk of PABC, so the family history of breast cancer should be assessed when studying PABC [43,44]. In our sample, more patients in the first-pregnancy group had a family history of breast cancer (10.1% in the first-pregnancy group vs. 8.9% in the nonpregnancy group); however,
whether this is related to the poor prognosis observed in this group requires further research.

The other part of our study classification divided the research population into three subgroups: the pregnancy (abortion) group, pregnancy (non-abortion) group and lactation group. Some scholars have proposed that there are two subtypes of PABC: breast cancer diagnosed during pregnancy and breast cancer diagnosed postpartum. The importance of this classification is emphasized because some epidemiological data indicate that postpartum cases may have specific deteriorating outcomes and that postpartum breast degeneration may increase the metastatic potential of PABC [45]; however, other studies present the opposite view that pregnancy was more detrimental [46]. In our study, the pregnancy group was subdivided into the pregnancy (abortion) group and pregnancy (non-abortion) group based on the different hormonal status and treatment methods of the groups to explore how pregnancy impacted DFS. The survival analysis results indicated that the pregnancy (abortion) group and the lactation group tended to have better survival rates than the pregnancy (non-abortion) group.

In our study, we found that patients in early pregnancy were more likely to terminate their pregnancies, while those in late pregnancy usually preferred to delay treatment until delivery of the fetus. Notably, the pregnancy (abortion) group tended to have smaller tumor sizes, less Ki–67 positivity, and a smaller proportion of TNBC, indicative of a good prognosis. Ki–67 is an independent prognostic factor for breast cancer [47], and TNBC has a higher rate of recurrence and worse prognosis than other breast cancer subtypes [48,49]. There are three possible reasons for the worse prognosis in the pregnancy (non-abortion) group. First, the poor prognosis was often because the mother in middle-late pregnancy chose not to receive treatment until the fetus was born to ensure normal fetal growth. Delayed treatment led to an increased risk of recurrence and distant metastasis. Second, the poor prognosis may be caused by fluctuating hormone levels and microenvironmental changes. Reproductive events can affect breast tissue differentiation through hormonal mechanisms. Estrogen levels increase steadily during pregnancy and peak in mid-late pregnancy. In addition, estrogen plays a variety of roles in tumor transformation in breast tissue, both as a carcinogen and as a tumor growth-inducing factor [50,2]. Furthermore, under the long-term influence of microenvironmental factors, such as growth factors, most patients in the pregnancy (non-abortion)
group had high HER-2 positivity rates and high Ki-67 expression during late pregnancy, which may have resulted in their poor prognosis [47].

Starting chemotherapy in mid-late pregnancy without delaying chemotherapy until after delivery is generally preferred, as unnecessary delays may result in a worse prognosis. FAC (fluorouracil, adriamycin and cyclophosphamide) is a commonly used chemotherapy regimen, and studies have shown that it is safe in mid-late pregnancy [51]. Doxorubicin and cyclophosphamide can be excreted through milk and are therefore prohibited during lactation [51]. However, in China, people generally do not undergo chemotherapy during mid-late pregnancy. Mid-pregnancy women with PABC choose to either terminate the pregnancy or delay chemotherapy until delivery, while late-pregnancy women usually start chemotherapy treatment after delivery. In our study population, 20 (30.3%) PABC patients with HER-2 positivity did not receive Herceptin treatment, 18 (85.7%) of whom were diagnosed with PABC before 2017. This may be because it was not until 2017 that Herceptin was included in the scope of medical insurance reimbursement in China. Before 2017, the high price of Herceptin restricted its use. Previous studies have also indicated that pregnant mothers cannot benefit from termination of pregnancy; therefore, it is not recommended for the purpose of improving prognosis [52,41]. However, in our study population, 23 (25.8%) patients diagnosed during pregnancy still had spontaneous or elective abortions. Nineteen (82.6%) of them were non-first pregnancies, which may have been because women who had already given birth to one baby were more likely to choose abortion.

It should be acknowledged that there were some limitations in our present study. First, the analysis was not adjusted for potential confounding factors, including age, tumor size and lymph node status, for the analysis of PABC survival. In addition, this study was a single-center study with a limited population, and the sample size enrolled in the study was not large enough to obtain a more reliable conclusion. However, the lack of statistically significant differences in the prognosis between the subgroups does not mean that we need to ignore the true relevance of these findings. Moreover, some information about the clinicopathological features of PABC is absent. HR status was lacking for 4 patients because their pathological biopsies from an external hospital were not promptly entered into
the electronic case system of our hospital 14 years ago. The HER-2 status of 9 people was unknown because the overexpression status of HER-2 in their tumors was unclear when detected by immunohistochemistry, and patients refused to undergo another biopsy for further FISH analyses due to the high cost at that time—up to approximately $350. Ki-67 information was lacking for 42 people because the clinical significance of Ki-67 was not realized more than a decade ago. Information about histological grades was lacking for 70 (34.5%) patients, which may be due to the reduction or even disappearance of tumor residuals after neoadjuvant chemotherapy.

In conclusion, PABC is an invasive disease with poor prognosis in young women, and because of fetal factors, women in mid-late pregnancy often choose to delay treatment until delivery. With the abolishment of China’s one-child policy, an increasing number of women are having more than one child, which underlies the upward trend in the occurrence of PABC. Our single-center study provides some information on the characteristics and survival rates of PABC patients. However, further research on PABC in a large population and investigations into the physiological mechanisms are needed in the future.

Declarations
Authors’ contributions
BH and HL conceived and designed the study. BH and HZ analyzed the data. XL and XH contributed reagents, materials, and analysis tools. BH and HZ wrote the paper. All authors read and approved the final manuscript.

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Compliance with Ethical Standards
Competing Interests The authors have declared that no competing interests exist.

Research involving human and animal participants This study did not involve animals.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964
Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This retrospective study was approved by the Ethics Committee Review Board of Fudan University Shanghai Cancer Center, who waived the need to obtain informed consent.

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Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Tables
Due to technical limitations, the table is only available as a download in the supplemental files section.

Figures
Figure 1

Molecular types of the total population (a), first pregnancy subgroup (b) and non-first pregnancy subgroup (c)
Molecular types of pregnancy (non-abortion) subgroup (a), lactation subgroup (b) and pregnancy (abortion) subgroup (c).

Figure 3

5-year disease free survival of first and non-first pregnancy subgroup.
Figure 4

5-year disease free survival of pregnancy (abortion) subgroup, pregnancy (non-abortion) and lactation subgroup

Supplementary Files

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