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Clinico-pathologic features, treatment and outcomes of breast cancer during pregnancy or the post-partum period

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Abstract

Purpose—Breast cancer during pregnancy (BC-P) or the first year post-partum (BC-PP) is rare and whether it differs from breast cancer (BC) in young women not associated with pregnancy is uncertain.

Methods—We queried our institutional database for BC-P and BC-PP cases and matched controls with BC not associated with pregnancy diagnosed between January 1, 1985 and December 31, 2013. We performed two parallel retrospective cohort studies evaluating clinico-pathologic features, treatment and outcomes for BC-P and BC-PP cases compared to their controls.

Results—In our population of 65 BC-P cases, 135 controls for BC-P cases, 75 BC-PP cases and 145 controls for BC-PP cases, high grade and estrogen receptor-negativity were more frequent in both case groups than their controls. Among those with stage I–III BC, patterns of local therapy were similar for both case groups and their controls, with the majority undergoing surgery and radiation. Over three-fourths of those with stage I–III BC received chemotherapy. BC-P cases

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Conflict of interest Ciara C. O'Sullivan has received research support from Lilly. Gary L. Rosner owns stock in Johnson & Johnson and Novartis. Gary L. Rosner is a member of an independent data monitoring committee for Novartis. Vered Stearns has received institutional research support from Abbvie, Biocept, Pfizer, Novartis, Medimmune, and Puma Biotechnology. Vered Stearns has served as a consultant for Iridium Therapeutics, Inc. Vered Stearns is a member of a data safety monitoring board for Immunomedics, Inc. Karen Lisa Smith's spouse with stock ownership in ABT Labs and Abbvie. Karen Lisa Smith has received research support from CancerIncite and Pfizer. The following authors declare that they have no conflicts of interest: Sheeba Irshad, Zheyu Wang, Zhuojun Tang, Christopher Umbricht and Mindy S. Christianson.

Research involving human participants and/or animals 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. We obtained approval from the Johns Hopkins (JH) institutional review board (IRB) to conduct this retrospective study.

tolerated chemotherapy well, with the majority receiving doxorubicin/cyclophosphamide every 3 weeks. On multivariate analyses of those with stage I–III BC, BC-P cases had non-significantly higher hazards of recurrence and death compared to their controls, while BC-PP cases had non-significantly lower hazards of recurrence and death compared to their controls.

Conclusion—BC-P and BC-PP were associated with adverse clinic-pathologic features in our population. However, we did not observe inferior outcomes for BC-P or BC-PP compared to controls, likely due to receipt of aggressive multi-modality therapy.

Keywords

Pregnancy; Post-partum; Breast cancer; Young women; Prognosis

Introduction

Pregnancy-associated breast cancer (PABC) is commonly defined as breast cancer (BC) during pregnancy (BC-P) or the first year post-partum (BC-PP) [1, 2]. Although rare, the incidence of PABC has risen and up to 15% of BC cases under age 35 are pregnancy-associated [3–6]. PABC is often characterized by adverse features, including estrogen receptor (ER)-negativity, high grade, large size and nodal involvement; however, it is uncertain whether these features differ from BC in young women not associated with pregnancy [7–14]. In addition, whether PABC carries a less favorable prognosis than non-PABC is uncertain [1, 2, 5, 9, 11, 12, 15–19]. Separating BC-P and BC-PP is important as BC-PP may carry a poorer prognosis [1, 2, 9, 13, 15, 19, 20].

Guidelines recommend that BC-P treatment adhere as closely as possible to standard BC treatment with chemotherapy considered safe after the first trimester. Cancer treatment and antenatal care must be coordinated with the goal of term delivery, individualizing sequencing according to oncologic needs and gestational age [21, 22]. Although doxorubicin and cyclophosphamide (AC) is commonly used for BC-P, few publications have described the clinical experience associated with this regimen during pregnancy [21, 23–28].

We present two parallel retrospective matched cohort analyses evaluating BC-P and BC-PP cases separately, each compared to matched controls with non-PABC. We describe treatment patterns of BC-P, especially the use of AC and the sequencing of cancer treatment and delivery.

Methods

Participant selection

After obtaining approval from the Johns Hopkins (JH) institutional review board (IRB), we identified cases and controls from the JH Integrated BC Research Database. Informed consent was not required for this retrospective study. Candidate participants were females diagnosed with ductal carcinoma in situ (DCIS) or invasive BC between January 1, 1985 and December 31, 2013 who attended at least one medical oncology appointment at JH and who had pathology reviewed at JH. We created two separate case groups (BC-P and BC-PP) and two separate control groups (controls for BC-P cases and controls for BC-PP cases). BC-P

cases were pregnant at diagnosis and BC-PP cases were diagnosed ≤ 365 days after delivery. To identify cases, we queried the database for candidate participants diagnosed with BC at age ≤ 45 years using the following search terms: pregnant, pregnancy, delivery, post-partum, partum, gestation, infant, baby, breastfeeding and lactation. After forming the case groups, we aimed to identify two controls for each case by randomly selecting from the candidate participants with non-PABC (defined as not being pregnant at diagnosis and having no delivery within 365 days before diagnosis). Each control was matched to a case according to age (± 5 years), extent of disease (DCIS, node-negative invasive BC, node-positive invasive BC or metastatic BC) and time period of diagnosis (1985–1999, 2000–2004 or 2005–2013). The categories for time period of diagnosis were selected based upon when major changes in breast cancer therapy occurred, such as the introduction of the sentinel node procedure in approximately 2000 and the incorporation of taxanes into adjuvant chemotherapy regimens in approximately 2004 [29, 30].

Information regarding demographics, tumor characteristics, treatment, family history, reproductive history, disease status (no evidence of recurrence, loco-regional recurrence or distant recurrence) and vital status was obtained by chart review. For BC-P cases, we reviewed available records regarding gestation at diagnosis, obstetric outcomes and sequencing of BC therapy and delivery. We considered women with a previous delivery as parous. The data that support the findings of this study are not publicly available as they contain information that could compromise individual patient privacy, however, they are available upon reasonable request from the corresponding author (KLS).

Statistical analysis

We used descriptive statistics to summarize patient, tumor and treatment characteristics. Each case group was compared to its control group using the Welch two-sample *t* test for continuous variables and the Pearson's Chi-square test for categorical variables. Exploratory analysis comparing the two case groups was performed. Comparisons of treatments received were limited to those with stage I–III BC. Statistical significance was based on a two-sided type-I error rate of 0.05.

We calculated recurrence free survival (RFS) from the time of diagnosis to the time of loco-regional or distant recurrence or death. We censored patients who remained alive without recurrence at the time of last known follow-up. We calculated overall survival (OS) from the time of diagnosis to the time of death from any cause. We censored those who remained alive at the last date they were known to be alive. Survival distributions were described using the Kaplan–Meier method. Stratified cox proportional hazards models stratified for our matching variables were used to estimate the hazard ratios (HR) with 95% confidence intervals (CI) for recurrence and death for each case group compared to its control group. Univariate and multivariate analyses were performed to evaluate other factors associated with recurrence and death, including ER status, receipt of chemotherapy, grade, margin status and stage. Analyses of RFS and OS were limited to patients with stage I–III BC.

Results

Study population

After excluding candidate participants who did not meet eligibility criteria, our study population included 140 cases (65 with BC-P and 75 with BC-PP) plus 280 controls (135 for BC-P cases and 145 for BC-PP cases) (Fig. 1). Due to limitations in the number of young candidate participants in our database, we could not identify two controls for each case.

Clinico-pathologic features

Over 70% of each group were stage II or higher. High grade and ER-negativity were more common in both case groups than their controls. Both case groups were less likely to receive all treatment at JH and had shorter follow-up than their controls. Approximately two thirds of each control group was parous. Despite matching, mean age was younger in both case groups than their controls. Tumor characteristics did not differ between the two case groups (Table 1).

Treatment of cases and controls with stage I–III breast cancer

There were no significant differences in the frequency of surgery, radiation, and receipt of chemotherapy between each case group and its control group. Over 75% of each case and control group received chemotherapy. Reconstruction and receipt of HER2-targeted therapy were less frequent among BC-P cases with stage I–III disease than their controls (Table 2). When limited to the HER2-positive subset of BC-P cases and their controls with stage I–III disease, we also observed less receipt of HER2-targeted therapy among cases. Three of ten (30%) of BC-P cases with Stage I–III HER2-positive breast cancer received HER2-targeted therapy compared to 13 of 23 (57%) controls for BC-P cases with stage I–III HER2-positive breast cancer. Receipt of endocrine therapy (ET) was less frequent among both case groups with stage I–III disease compared to their controls (Table 2). When limited to cases and controls with stage I–III ER-positive disease, we also observed less receipt of ET among cases. Of 20 BC-P cases with stage I–III ER-positive breast cancer, 8 (40%) received ET compared to 56 of 81 (60%) controls for BC-P cases with stage I–III ER-positive breast cancer. Similarly, of 27 BC-PP cases with stage I-III ER-positive breast cancer, 13 (48%) received ET compared to 67 of 89 (75%) of controls for BC-PP cases with stage I–III ER-positive breast cancer. We observed no differences in breast conservation rates, margins and use of sentinel node procedure across groups.

Multi-disciplinary management of BC-P cases

Obstetric outcome was known for 43% of BC-P cases. Of 17 known live births, 6 were via vaginal delivery and 11 via cesarean sections. Labor was induced during the third trimester in 11 BC-P cases and 9 births were pre-term. Sequencing of BC treatment and delivery was variable, with 20 women undergoing surgery and 20 receiving chemotherapy while pregnant. Of those treated with chemotherapy during pregnancy, 15 received AC every 3 weeks. No BC-P cases received dose dense AC during pregnancy. One BC-P case with metastatic BC received a taxane during pregnancy and two received myeloid growth factors during

pregnancy. Complications associated with receipt of AC during pregnancy were uncommon and included one maternal infection and one neonate with cytopenias (Table 3).

Recurrence and survival of cases and controls with stage I–III breast cancer

Median follow-up exceeded 4 years for all participants, but was shorter for cases than their controls (Table 1). RFS and OS decreased over time with no statistically significant differences observed between each case group and its controls (Fig. 2). Five-year RFS was 51% among BC-P cases, 60% among controls for BC-P cases, 63% among BC-PP cases and 74% among controls for BC-PP cases. In univariate analysis, there were slightly higher hazards of recurrence for BC-P cases than their controls (HR 1.43, 95% CI 0.70–2.93, Table 4) and for BC-PP cases than their controls (HR 1.43, 95% CI 0.69–3.00, Table 5) although these did not reach statistical significance. Distant recurrences were more common than loco-regional recurrences, representing 58% and 60% in BC-P cases and their controls, respectively; and 78% and 57% in BC-PP cases and their controls, respectively. Five-year OS was 75% among BC-P cases, 81% among controls for BC-P cases, 81% among BC-PP cases and 87% among controls for BC-PP cases. In univariate analysis, the hazard of death was almost twice as high for BC-P cases than their controls (HR 1.91, 95% CI 0.70–5.21, Table 4) and was slightly higher for BC-PP cases than their controls (HR 1.39, 95% CI 0.56–3.47, Table 5), however, these differences did not reach statistical significance.

After adjusting for the pre-specified covariates, there were non-significant but higher hazards of recurrence and death for BC-P cases than their controls (multivariate HR for recurrence 1.51, 95% CI 0.56–4.06; multivariate HR for death 2.85, 95% CI 0.57–14.29). Other covariates were not significantly associated with recurrence or death for BC-P cases and their controls on multivariate or univariate analysis (Table 4). After adjusting for the pre-specified covariates, there were non-significant but lower hazards of recurrence and death for BC-PP cases than their controls (multivariate HR for recurrence 0.81, 95% CI 0.26–2.52; multivariate HR for death 0.57, 95% CI 0.13–2.58). In univariate analyses among BC-PP cases and their controls, higher grade was associated with threefold higher risk of recurrence and higher stage was associated with threefold higher risk of death, but these associations were not statistically significant on multivariate analyses (Table 5).

Discussion

BC in young women is associated with adverse features [10]. Whether PABC differs from non-PABC in young women and whether BC-P and BC-PP differ from one another has been unclear, potentially due to limitations of prior studies, including small sample size, inconsistent control populations, variable definitions of PABC, lack of consideration of the effects of treatment on outcomes, and grouping BC-P and BC-PP together [1, 2, 5, 7–13, 15–19]. We report here results of a large retrospective study with long follow-up and comprehensive treatment information in which we considered BC-P and BC-PP separately. We observed that both BC-P and BC-PP are frequently ER-negative and high grade. However, these differences did not translate into statistically significantly inferior outcomes for BC-P or BC-PP cases compared to matched controls with non-PABC. We did, however,

observe non-significant but higher hazards of recurrence and death for BC-P cases than their controls.

In a meta-analysis of 30 studies, Azim et al. concluded that PABC carries a higher risk of recurrence and death than non-PABC, with especially poor outcomes for BC-PP [1] An updated meta-analysis of 41 studies by Hartman et al. reached a similar conclusion [2]. Some have suggested that the negative impact of a post-partum diagnosis on prognosis extends to 5 or even 10 years after delivery [2, 9, 13, 15, 19, 31]. Changes in the post-partum breast microenvironment associated with breast involution, such as immune cell influx, extracellular matrix remodeling, and lymphangiogenesis may explain these unfavorable outcomes [9, 20]. Given the apparent differences between BC-P and BC-PP, we considered them separately in this study, however, we did not confirm the finding that PABC, especially BC-PP, is associated with significantly inferior outcomes compared to non-PABC. Almost all participants with stage I–III BC in our study underwent surgery and over 75% received chemotherapy, suggesting that aggressive multi-modality treatment may overcome the adverse biologic features of PABC.

Women were eligible to be controls in our study if they had not had a delivery within one year of diagnosis. Approximately two thirds of our controls were parous, thus, it is conceivable that some had "late post-partum" BC diagnosed more than one year after delivery. If these women carried poor prognosis based on late post-partum diagnosis, their inclusion in our control groups may have masked our ability to detect differences in outcomes between our cases and controls [2, 9, 13, 15]. To avoid this limitation, we suggest that future PABC studies limit eligibility for controls to nulliparous women or those with remote prior deliveries.

In keeping with previous reports, we observed that PABC cases were less likely to receive ET than controls [11, 12, 21, 22, 32]. It is possible this finding reflects missing data due to delayed initiation of ET in women with PABC. We do not think this finding is attributable to lower rates of ER-positive disease among women with PABC as rates of receipt of ET were lower among BC-P and BC-PP cases than their controls even when the analysis was limited to the stage I-III ER-positive subpopulation. Ensuring women with ER-positive PABC receive ET is important as the majority of young women with BC have ER-positive disease and outcomes are the least favorable among this subset [33]. We also observed that BC-P cases were less likely to receive HER2-targeted therapy and reconstruction. These findings may also reflect incomplete ascertainment of delayed therapies. In addition, low rates of receipt of HER2-targeted therapy in our study population may be partly explained by the fact that some cases and controls were diagnosed prior to publication of the adjuvant trastuzumab trials [34–36]. Other than avoiding chemotherapy during the first trimester and delaying initiation of ET, HER2-targeted therapy and radiation until after delivery, treatment of BC-P should adhere to standard BC therapy [21, 22] and efforts to ensure delivery of ET and HER2-targeted therapy are of paramount importance.

Consistent with guidelines supporting administration of chemotherapy after the first trimester, we report the safety of AC during pregnancy [21, 22]. Our findings add to the available literature regarding chemotherapy for BC-P, the majority of which focuses on use

of 5-fluorouracil-based regimens [23–25]. At this time, data remain limited regarding taxanes and dose dense (every 2 weeks) therapy with growth factor support during pregnancy, although recent guidelines support consideration of these therapies [21, 26–28]. It is notable that the majority of BC-P cases in our study population received AC every 3 weeks. We do not know if this schedule was selected due to lack of comfort using growth factors during pregnancy or based on the need to spread chemotherapy out over a longer period of time since many BC-P cases were diagnosed early in pregnancy. In general, data indicates superior outcomes with the use of dose dense therapy compared to every 3 week therapy, so it is possible this regimen negatively impacted outcomes [37].

Sequencing of BC care and delivery were variable in our population, emphasizing the need to individualize management based on gestational age and oncologic considerations [21, 22]. Induction of labor, pre-term delivery and cesarean section was not uncommon among our BC-P cases. Prenatal exposure to chemotherapy is associated with increased premature rupture of membranes, premature labor and pre-term delivery, although, as we observed, pre-term delivery in women with BC-P is often iatrogenic [21, 23, 38–40]. Children exposed to chemotherapy in utero generally experience normal cognitive development adjusted for gestational age at birth. However, prematurity negatively impacts cognitive development, thus, it is optimal to deliver as close to term as possible [16, 21, 25, 39, 41]. Some literature suggests delays in diagnosis, initiation of therapy and interruptions of therapy in women with BC-P may contribute to more advanced stage at diagnosis and to poorer outcomes [32, 42]. Unfortunately, we were unable to capture delays in diagnosis and treatment in our study population.

It is now well accepted that breast cancer surgery can be performed in pregnant women, even during the first trimester. Mastectomy should not be recommended solely because of pregnancy and breast-conserving surgery should be considered if feasible. Similarly, axillary lymph node dissection is not required solely because of pregnancy as sentinel node biopsy, preferably with radioactive tracer, can be performed during pregnancy [21, 43]. In line with published guidelines on the surgical management of breast cancer during pregnancy, we observed no differences in breast conservation rates, margins and use of the sentinel node procedure across groups. Notably, immediate reconstruction was less frequent among BC-P cases than their controls. This, too, is in keeping with published guidelines that discourage immediate reconstruction during pregnancy, although there is some data regarding immediate expander placement [21, 43]. It is noteworthy that our data did not capture reconstruction after delivery and delayed implant placement is recommended for women diagnosed with breast cancer during pregnancy [43].

Weaknesses of our study include inclusion of parous controls, retrospective single institution design, incomplete data (especially regarding obstetric outcomes, receipt of adjuvant ET, receipt of adjuvant HER2-targeted therapy, delays and gaps in treatment), differences in mean age between case and control groups despite matching, shorter follow-up for cases than controls, differences in treatment location and possible incomplete ascertainment of cases from our database. In addition, we were unable to evaluate the association of race and socioeconomic status with recurrence and death in our study population. Cancer mortality rates are higher among blacks and among individuals of lower socioeconomic status [44].

Our case and control groups were well-balanced with regard to race but, owing to limitations in patient numbers, we were unable to formally test the association of race with outcomes in our multivariate models. Unfortunately, information about socioeconomic status for our study population was not available, thus, we could not evaluate the association of this important variable with outcomes. Similarly, we were unable to evaluate the association of adherence to adjuvant ET to outcomes in our cases and controls as this information was not available. Non-adherence is more common among young breast cancer patients and is associated with increased breast mortality, thus, lack of consideration of the impact of adherence on outcomes is a limitation of our study [45, 46]. Notably, 27% of our study population received care exclusively at other institutions, likely contributing to missing data regarding adjuvant therapies and long term outcomes and potentially also contributing to differences in outcomes if patterns of care differed across treatment locations. However, we feel that our population is representative of the general United States cancer population for whom much of cancer care is delivered in community settings [47].

In conclusion, we found that, despite adverse characteristics, outcomes were not statistically significantly inferior for PABC compared to non-PABC in our population; a finding that we think is likely a reflection of aggressive multi-modality treatment. However, BC recurrence and death were not uncommon in our population, consistent with previous data demonstrating unfavorable outcomes for young women with BC [10]. In addition, there were non-significant but higher hazards of recurrence and death for BC-P cases than their controls, thus, it is possible that with more power, we may have detected a significant difference in outcomes between our PABC cases and their controls. In particular, suboptimal treatment due to delay or incomplete administration of adjuvant therapies may negatively impact outcomes in women with PABC. Moving forward, larger multi-institutional efforts to study outcomes and efforts to ensure optimal treatment delivery are important for women with PABC. The interaction between reproductive factors and BC is complex and expanded efforts to collect reproductive histories and to explore the biology of BC in young women are needed. Further study of the pregnant and post-partum breast microenvironment may define pathways implicated in tumorigenesis and metastasis, facilitating development of agents for prevention and treatment [48, 49].

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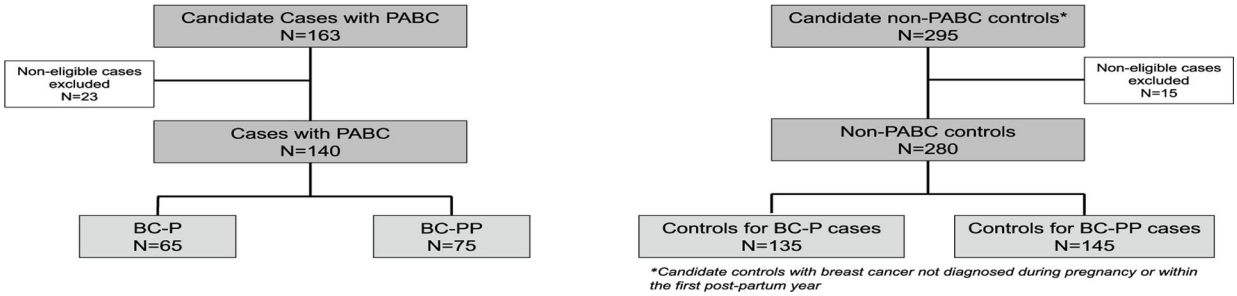

Fig. 1.

Consolidated standards of reporting trials (CONSORT) diagram of study population

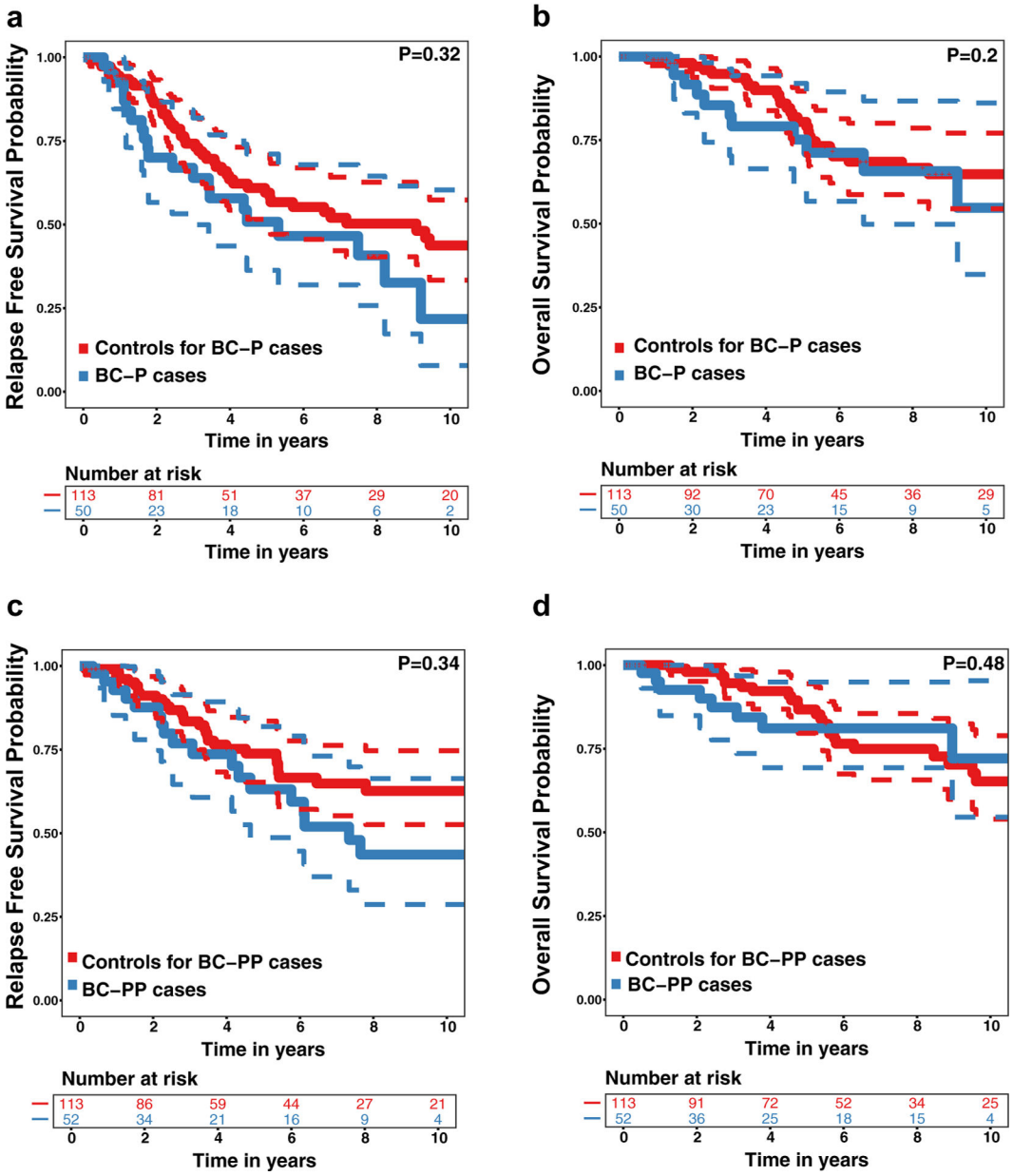

Fig. 2.

Recurrence Free Survival (RFS) and Overall Survival (OS) (with 95% confidence intervals) for Cases with Stage I–III Pregnancy-Associated Breast Cancer and Their Controls. **a** RFS for women with breast cancer diagnosed during pregnancy (BC-P cases) and their controls, **b** OS for BC-P cases and their controls, **c** RFS for women with breast cancer diagnosed during the first year post-partum (BC-PP cases) and their controls, **d** OS for BC-PP cases and their controls

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Table 1

Patient and tumor characteristics

Characteristic	BC-P cases *N* = 65	Controls for BC-P cases *N* = 135	BC-PP cases *N* = 75	Controls for BC-PP cases *N* = 145	*P* value for comparison of BC-P cases to their controls[b]	*P* value for comparison of BC-PP cases to their controls[b]	*P* value for comparison of BC-P cases to BC-PP cases[b]
Mean age at diagnosis in years (SD)	34.5 (5.0)	36.7 (5.3)	34.7 (3.8)	37.2 (4.7)	0.007	< 0.001	0.83
Treatment location (*N*, %)							
Johns Hopkins	9 (14%)[a]	25 (19%)	7 (9%)	35 (24%)	< 0.001	< 0.001	0.65
Another institution	30 (46%)	24 (18%)	34 (45%)	25 (17%)			
Both	26 (40%)	82 (63%)	34 (45%)	84 (58%)			
Year of diagnosis (*N*, %)							
1985–1989	1 (2%)	4 (3%)	1 (1%)	3 (2%)	0.83	0.28	0.99
1990–1994	2 (3%)	7 (5%)	3 (4%)	13 (9%)			
1995–1999	9 (14%)	17 (13%)	9 (12%)	11 (8%)			
2000–2004	26 (40%)	49 (37%)	3 (40%)	47 (33%)			
2005–2009	13 (20%)	20 (15%)	13 (17%)	40 (28%)			
2010–2014	14 (22%)	36 (27%)	19 (25%)	30 (21%)			
Race (*N*, %)							
White	42 (67%)	97 (73%)	59 (79%)	97 (67%)	0.52	0.43	0.35
Black	15 (24%)	28 (21%)	11 (15%)	34 (24%)			
Asian	1 (2%)	3 (2%)	2 (3%)	3 (2%)			
Other	5 (8%)	4 (3%)	3 (4%)	9 (6%)			
Unknown	0 (0%)	1 (1%)	0 (0%)	1 (1%)			
Stage (*N*, %)							
0 (DCIS)	3 (5%)	4 (3%)	3 (4%)	4 (3%)	0.81	0.68	0.30
I	10 (15%)	27 (20%)	11 (15%)	34 (23%)			
II	26 (40%)	53 (39%)	25 (33%)	46 (32%)			
III	14 (22%)	33 (24%)	16 (21%)	33 (23%)			
IV	7 (11%)	10 (7%)	20 (17%)	25 (17%)			
Unknown	5 (8%)	8 (6%)	5 (7%)	3 (2%)			
Grade (*N*, %)							

Characteristic	BC-P cases *N* = 65	Controls for BC-P cases *N* = 135	BC-PP cases *N* = 75	Controls for BC-PP cases *N* = 145	*P* value for comparison of BC-P cases to their controls[b]	*P* value for comparison of BC-PP cases to their controls[b]	*P* value for comparison of BC-P cases to BC-PP cases[b]
1	1 (2%)	11 (9%)	2(3%)	8 (6%)	0.017	0.008	0.60
2	14 (22%)	41 (34%)	11 (16%)	46 (34%)			
3	49 (77%)	69 (57%)	57 (81%)	81 (60%)			
ER-positive (*N*, %)	29 (51%)	94 (72%)	42 (63%)	111 (80%)	0.004	0.006	0.19
HER2-positive (*N*, %)	13 (25%)	27 (27%)	19 (33%)	25 (23%)	0.77	0.14	0.31
Family history of breast or ovarian cancer (*N*, %)	28 (47%)	54 (46%)	32 (47%)	60 (44%)	0.91	0.69	0.97
Age at Menarche in years (*N*, %)							
≤10	2 (8%)	4 (6%)	4 (9%)	5 (6%)	0.25	0.39	0.68
11	2 (8%)	6 (9%)	8 (19%)	14 (18%)			
12	10 (38%)	13 (20%)	16 (37%)	19 (24%)			
13	7 (27%)	14 (22%)	7 (16%)	29 (23%)			
≥14	5 (19%)	27 (42%)	8 (19%)	18 (23%)			
Parity at diagnosis (*N*, %)							
0	21 (34%)	41 (33%)	0 (0%)	44 (33%)	0.51	< 0.001	< 0.001
1–3	38 (61%)	79 (63%)	65 (92%)	80 (60%)			
4–5	1 (2%)	5 (4%)	5 (7%)	6 (4%)			
≥6	2 (3%)	1 (1%)	1 (1%)	4 (3%)			
Mean duration of follow-up in months (SD)	50.9 (51.9)	78.4 (66.0)	55.8 (55.6)	72.8 (61.1)	0.002	0.04	0.59

[a] All percentages based on non-missing values

[b] *P* values for *t* tests and Chi-squared tests performed on non-missing proportions

Table 2

Treatment characteristics of cases and controls with stage I-III breast cancer

Characteristic	BC-P cases *N* = 50	Controls for BC-P cases *N* = 113	BC-PP cases *N* = 52	Controls for BC−PP cases *N* = 113	*P* value for comparison of BC−P cases and their controls[b]	*P* value for comparison of BC−PP cases and their controls[b]	*P* value for comparison of BC−P cases to BC−PP cases[b]
Breast surgery(*N*, %)							
Mastectomy	33 (67%)[a]	81 (74%)	32 (65%)	65 (58%)	0.42	0.39	0.83
Breast conservation	16 (33%)	29 (26%)	17 (35%)	47 (42%)			
Margins (*N*, %)							
Positive	4 (9%)	5 (4%)	2 (4%)	4 (4%)	0.21	0.78	0.17
Negative	34 (74%)	96 (86%)	41 (89%)	96 (86%)			
Close	8 (17%)	11 (10%)	3 (7%)	11 (10%)			
Nodal evaluation (*N*, %)							
None	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.18	0.67	0.20
Sentinel node biopsy	8 (19%)	35 (32%)	14 (30%)	37 (34%)			
Axillary node dissection	35 (81%)	72 (67%)	32 (70%)	72 (66%)			
Reconstruction (*N*, %)							
None	30 (75%)	47 (47%)	21 (51%)	62 (58%)	0.01	0.73	0.08
Implant	5 (12%)	28 (28%)	11 (27%)	23 (21%)			
Autologous	5 (12%)	24 (24%)	9 (22%)	22 (21%)			
Radiation (*N*, %)	28 (78%)	64 (65%)	30 (77%)	66 (70%)	0.17	0.43	0.93
(Neo)adjuvant chemotherapy (*N*, %)	40 (80%)	89 (83%)	40 (78%)	84 (86%)	0.63	0.26	0.85
Endocrine therapy (*N*, %)	14 (48%)	61 (86%)	21 (75%)	72 (92%)	< 0.001	0.02	0.04
HER2-targeted therapy (*N*, %)	5 (22%)	14 (54%)	7 (33%)	8 (36%)	0.02	0.84	0.39

[a] All percentages based on non-missing values

[b] *P* values for Chi-squared tests performed on non-missing proportions

Table 3

Multi-disciplinary management of 65 cases with breast cancer diagnosed during pregnancy

Characteristic	*N* (%)
Trimester at diagnosis	
1	26 (40%)
2	13 (20%)
3	17 (26%)
Missing	9 (14%)
Obstetric outcome	
Elective termination	7 (11%)
Spontaneous abortion	4 (6%)[b]
Pre-term delivery	9 (14%)
Term delivery	7 (11%)
Post-dates delivery	1 (2%)
Missing	37 (57%)
BC[a] therapy during pregnancy	
Chemotherapy	20 (31%)[c]
Endocrine therapy	0 (0%)
Radiation	0 (0%)
HER2−targeted therapy	0 (0%)
Surgery	20 (31%)
Sequencing of BC treatment and delivery	
Delivery → Cancer therapy	10 (15%)
Breast cancer surgery → Delivery ± → Adjuvant systemic therapy	8 (12%)
Neoadjuvant chemotherapy → Delivery ± → Further breast cancer therapy	8 (12%)
Breast cancer surgery → Adjuvant chemotherapy → Delivery ± → Further adjuvant systemic therapy	12 (18%)
Missing	27 (42%)
Maternal complications	
Infection	2 (3%)[c,d]
Pre-eclampsia	3 (5%)

Characteristic	*N* (%)
Hemorrhage	1 (2%)
Fetal/neonatal complications	
Intrauterine growth retardation	1 (2%)[c]
Malpresentation	2 (3%)
Cytopenias at birth	1 (2%)[e]

[a] *BC* breast cancer

[b] One spontaneous abortion occurred during AC

[c] Only the percentage of BC-P cases who received each type of treatment during pregnancy or in whom each type of complication occurred is reported

[d] One maternal infection occurred during AC

[e] The neonate with cytopenias at birth was born to a mother receiving AC

Table 4

Factors associated with recurrence and death among cases with stage i–iii breast cancer diagnosed during pregnancy and their controls

	Recurrence						Death					
	Univariate			Multivariate			Univariate			Multivariate		
	HR[a]	95% CI[b]	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Case versus control	1.43	0.70–2.93	0.32	1.51	0.56–4.06	0.41	1.91	0.70–5.21	0.20	2.85	0.57–14.29	0.20
Stage	1.34	0.69–2.61	0.38	2.14	0.83–5.51	0.11	1.33	0.55–3.24	0.53	2.21	0.53–9.21	0.28
Grade	0.89	0.49–1.61	0.71	1.10	0.50–2.45	0.81	1.39	0.61–3.16	0.44	1.24	0.41–3.74	0.71
ER-positive	1.37	0.55–3.41	0.50	1.16	0.41–3.32	0.78	0.51	0.13–1.94	0.32	0.38	0.08–1.84	0.23
Negative margins	0.99	0.38–2.62	0.99	1.11	0.30–1.08	0.88	1.15	0.31–4.41	0.84	0.93	0.15–5.59	0.94
Receipt of chemotherapy	0.67	0.23–1.98	0.47	0.50	0.10–2.53	0.40	1.50	0.31–7.20	0.61	1.08	0.11–10.45	0.95

[a] *HR* hazard ratio

[b] *CI* confidence interval

Table 5

Factors associated with recurrence and death in cases with stage i-iii breast cancer diagnosed during the first year post-partum and their controls

	Recurrence						Death					
	Univariate			Multivariate			Univariate			Multivariate		
	HR[a]	95% CI[b]	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Case versus control	1.43	0.69–3.00	0.34	0.81	0.26–2.52	0.72	1.39	0.56–3.47	0.48	0.57	0.13–2.58	0.47
Stage	1.74	0.83–3.65	0.14	1.17	0.39–3.49	0.77	3.27	1.05–10.13	0.04	5.33	0.60–47.54	0.13
Grade	3.00	1.12–8.04	0.03	3.30	0.86–12.65	0.08	1.53	0.46–5.12	0.49	3.13	0.32–30.44	0.33
ER-positive	0.45	0.17–1.17	0.10	0.55	0.14–2.11	0.38	0.27	0.07–1.03	0.06	0.59	0.08–4.27	0.60
Negative margins	0.58	0.13–2.50	0.46	1.11	0.21–5.76	0.90	0.43	0.07–2.46	0.34	0.34	0.02–6.76	0.48
Receipt of chemotherapy	1.17	0.31–4.35	0.82	0.53	0.06–4.84	0.57	0.58	0.08–4.30	0.59	0.15	0.003–6.86	0.33

[a] *HR* hazard ratio

[b] *CI* confidence interval