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Obstetric complications at time of delivery amongst breast cancer survivors: A population-based cohort study

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ABSTRACT

Purpose: Our aim was to determine whether breast cancer survivors are at increased risk of obstetric and maternal complications at time of delivery.
Methods: The USA 'National Inpatient Sample' database was queried for hospitalizations associated with deliveries, between 2015 and 2018. The incidence of maternal and fetal complications was compared between women with, and without, a personal history of breast cancer.
Results: Of the 2,103,216 birth related admissions, 617 (0.03%) of the women were breast cancer survivors, with the proportion increasing over time (from 0.02% in 2015 to 0.04% in 2018). Breast cancer survivors had a higher socioeconomic status ($p < 0.001$) and were significantly older compared to other mothers (34 vs. 28 years, $p < 0.001$). Additionally, they were more likely to suffer from preexisting chronic diseases including cardiopulmonary disease and diabetes mellitus, and had a higher incidence of multiple gestation (4.4% vs. 1.6%) [OR 2.7, 95% CI 1.9–4.0, $p < 0.001$]. The incidence of acute adverse events at time of delivery including fetal distress, preterm labor, cesarean section and maternal infection was higher amongst the breast cancer survivors. On multivariate analysis age, ethnic group, comorbidities, multiple gestations, and a previous breast cancer diagnosis, but not cancer treatment, were associated with an increased risk of an obstetric adverse event.
Conclusion: Breast cancer survivors have more comorbidities and are at increased risk of acute obstetrical complications at time of delivery. Further studies are required to validate these findings, and evaluate the ability of interventions to improve obstetrical outcomes amongst breast cancer survivors.

1. Introduction

Breast cancer in women of reproductive age is uncommon. It is estimated that the cumulative risk of being diagnosed with breast cancer by age 40 is approximately 0.5% [1,2]. Breast cancers arising in younger women often bear more aggressive features compared with those seen in older women, including high grade, triple-negative phenotype, HER2 over-expression, lympho-vascular invasion, and lymphocytic infiltration [3–6]. Therefore, even though age in itself is not an indicator for more aggressive treatments [7,8], younger breast cancer patients are often treated with more aggressive systemic protocols due to the nature of their disease [9]. Additionally, chemotherapy is associated with nearly twice the relative reduction in breast cancer mortality among women younger than 50 years as compared with older women, suggesting that even in younger patients with intermediate genomic risk breast cancer, chemotherapy is important, possibly due to the beneficial effects of chemotherapy-induced menopause [10]. Young patients not receiving chemotherapy, are often treated with endocrine therapy and ovarian function suppression for additional therapeutic benefit [11,12]. Hence premature menopause often results from breast cancer treatments,

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especially if chemotherapy is given to patients who are older than 40 years of age, while younger patients often experience amenorrhea for a period that increases with age, affecting their future reproductive potential. Hence, it is compulsory that young patients be counselled about the potential impact of treatment on their fertility and offered fertility preservation [7,13]. However, little is known about maternal and obstetric complications in this unique population [14]. Retrospective data suggest that there is no detrimental effect of pregnancy in breast cancer survivors on oncological outcome [15–19], however it is mandatory to quantify potential maternal and obstetric complication rates in this population to guide patients and medical teams. The objective of this study was to quantify the risk of major obstetric complications amongst breast cancer survivors (BCSur group) using a large population-based database.

2. Methods

The analysis was based upon data retrieved from the Nationwide Inpatient Sample (NIS) developed for the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality (AHRQ; Rockville, MD). The NIS collects administrative and clinical data on U.S. hospital discharges [20]. The most recent available NIS dataset contains discharge data from 1050 hospitals in 44 states, approximating a 20% stratified sample of all non-federal hospitals, with 5–8 million hospital discharges per year. The state agencies that contributed to the database are listed at www.hcup-us.ahrq.gov/hcupdatapartners.jsp. Information available from the NIS includes demographic information, up to 40 medical diagnoses (based upon ICD-10-CM) and 25 procedure codes for each hospitalization, geographic region, hospital characteristics, and payer information. The NIS incorporates all types of hospitals, all payers including the uninsured, and all ages. Post-discharge follow-up information is not available.

Inclusion criteria for the study were maternal hospitalizations associated with labor and delivery, between the last quarter of 2015 and the end of 2018. Delivery encounters were identified based upon the validated methodology developed by Clapp et al. [21] as applied to the first 15 listed diagnoses and procedures. To exclude double counting, women transferred to another hospital were excluded, however the delivery at the original hospital encounter was included. A woman was defined as a breast cancer survivor if code "*Z85.3 Personal history of malignant neoplasm of breast*" was included within the diagnoses. In-situ neoplasms of breast, i.e., DCIS and LCIS, were not included within this definition.

The diagnostic and procedure codes used to define obstetric complications and cancer diagnoses are listed in online Appendices Tables A1 - A3, based upon the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), the International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS), the Clinical Classifications Software Refined (CCSR) for ICD-10-CM diagnoses (v2021.1) and Diagnosis Related Group (DRG) for the date of discharge as assigned by the Medicare DRG Grouper algorithm during Healthcare Cost and Utilization Project (HCUP) database processing. Additional data extracted included age, previous caesarean section, race/ethnicity, and socioeconomic status (SES). Race/ethnicity was defined as White, Black, Hispanic, Asian/Pacific Islander, or other per NIS database coding. The categorical variable median household for patient's ZIP code (ZIPINC) indicates the median household income of the patient's ZIP code of residence. The median income values are 1999 estimates derived from projections from 1990 census values for block groups. The categories are defined so that the maximum for category 1 ($25,000) is approximately 150% of the 1999 poverty level and the boundary between the second and third categories ($35,000) is approximately the national median household income.

A binary composite variable was created recording the occurrence of one or more of the following adverse obstetric events: poor intrauterine growth, fetal malposition, fetal distress, eclampsia (including pre-eclampsia and gestational associated hypertension), maternal exhaustion, cesarean section, preterm labor, hemorrhage, other fetal problems, operative vaginal delivery, abruption, and fetal death. Likewise, a binary composite indicator variable was created representing the presence of any one or more of the following acute maternal medical events: infections, renal events, cardiac events, respiratory events, or vascular events. Statistical tests employed included Student's *t*-test, Pearson's Chi squared test and logistic regression; all statistical tests were two-sided and considered significant if p-value <0.05. Variables with a $p < 0.1$ on univariate analysis were included in multivariate analyses. Per database rules to assure patient privacy, findings with patient numbers of 10 or less are not reported in this paper. Statistical analysis was performed using Stata statistical package, version IC 16.1 (Stata, College Station, TX).

3. Results

Of the 2,103,216 birth related admissions between the last quarter of 2015 and the end of 2018, 617 (0.03%) of the women were breast cancer survivors (BCSur group). Clinical and demographic characteristics of the study population are presented in Table 1. The numbers of women who are BCSur at time of childbirth admission per 100,000 deliveries increased over the study period, similar trends were found per ethnic group, except Hispanics BCSur (Figs. 1 and 2). BCSur group was more likely to be older compared to the population without a history of breast cancer (non-BCSur) (median age 34 years vs. 28 years, $p < 0.001$). For both groups, the median age increased over this short period with a larger increase in the BCSur group compared to non-BCSur (Fig. 3).

Of the total population included, 50.5% were White, 19.9% Hispanic, 14% Black, 5.7% Asian/Pacific Islander, 5.1% other or unknown. Compared to the other ethnic groups, a smaller proportion of Hispanic origin were BCSurs [OR 0.5, 95% confidence interval (CI) 0.39–0.65, $p < 0.001$ (Table 1, Fig. 2). Household income, based upon patient ZIP Code, stratified according to the ethnic group, indicated a larger proportion of BCSur with high household income in the Asian/Pacific Islander and White compared to Black and Hispanic groups (Fig. 4). Overall, the BCSur group had a higher predicted socioeconomic status compared to the non-BCSur group (Table 1).

The BCSur group were more likely to have pre-existing chronic diseases compared to the non-BCSur group (Table 2, ICD-10 codes are listed in the Appendices), and more maternal infections at time of childbirth (Table 3).

Of the total population, 33,756 (1.6%) of the deliveries were for multiple gestations; 1.6% of the non-BCSur group (33,729 out of 2,102,599) and 4.4% of the BCSur group (27 out of 617), [OR 2.7,95% CI 1.9–4, p< <0.001]. There was a strong relationship between increasing maternal age and multiple gestations ($p < 0.001$).

Fetal distress, preterm labor, cesarean section and maternal infraction were more frequent in the BCSur group (Table 3). There were numerically fewer fetal intrauterine deaths amongst BCSur compared to the general population, however this was not statistically significant ($p = 0.08$) (Table 3).

On univariate analysis, multiple factors (Table 4) were associated with the occurrence of one or more adverse obstetric outcomes, including multiple gestations, older age, non-White ethnic group, various chronic medical conditions, and drug-tobacco-alcohol use (OR 1.3). A personal history of breast cancer was associated with an increased risk of an adverse obstetric outcome with an OR of 1.6, rising to an OR of 2.5 for those who had previously undergone radiation therapy or chemotherapy. There were also an association with estimated median household income, with lower estimated social-economic status (SES) patients having more complications. On multivariate analysis the same associations held, except that there was no longer an association with previous radiation therapy or chemotherapy. Similar associations were noted for maternal complications (Table 5), once again breast cancer, but not previous radiation therapy or chemotherapy, was

Table 1
Demographic and socioeconomic information of the study population.

	Total	Non-BCSur group	BCSur group	OR	[95%] CI	p value
n	2,103,216	2,102,599	617			
Median age	28	28	34	1.21	1.19–1.23	**<0.001**
Race						
White	1,062,223	1,061,863	360 (0.03%)	1		
% White	50.5	50.5	58.3			
Black	294,677	294,580	97 (0.03%)	0.97	0.78–1.22	0.799
%Black	14	14	15.7			
Hispanic	417,492	417,421	71 (0.017%)	0.50	0.39–0.65	**<0.001**
%Hispanic	19.9	19.9	11.5			
Asian/Pacific Islander	119,978	119,934	44 (0.03%)	1.08	0.79–1.48	0.621
% Asian/Pacific Islander	5.7	5.7	7.1			
Other	107,654	107,628	26 (0.024%)	0.71	0.48–1.06	0.095
%Other	5.1	5.1	4.2			
Median annual household income quartile for patient's ZIP Code						
Median ZIP income	2	2	3	1.33	1.23–1.42	**<0.001**
Medical costs coverage						
Medicare aid	930,355	930,167	188	1		
%Medicare aid	44.2	44.2	30.5			
Private	1,059,941	1,059,541	400	1.87	1.57–2.22	**<0.001**
%Private	50.4	50.4	64.8			
Self-pay/no charge	52,193	52,181	12	1.14	0.63–2.04	0.665
%Self-pay/no charge	2.5	2.5	1.9			
Other	58,157	58,140	17	1.45	0.88–2.38	0.145
%Other	2.8	2.8	2.8			

OR- odds ratio, OR > 1, indicates that the characteristic was overly-represented amongst the women with a personal history of breast cancer.
CI- confidence interval; BCSur- breast cancer survivor. P- value of statistically significant results is in bold font.

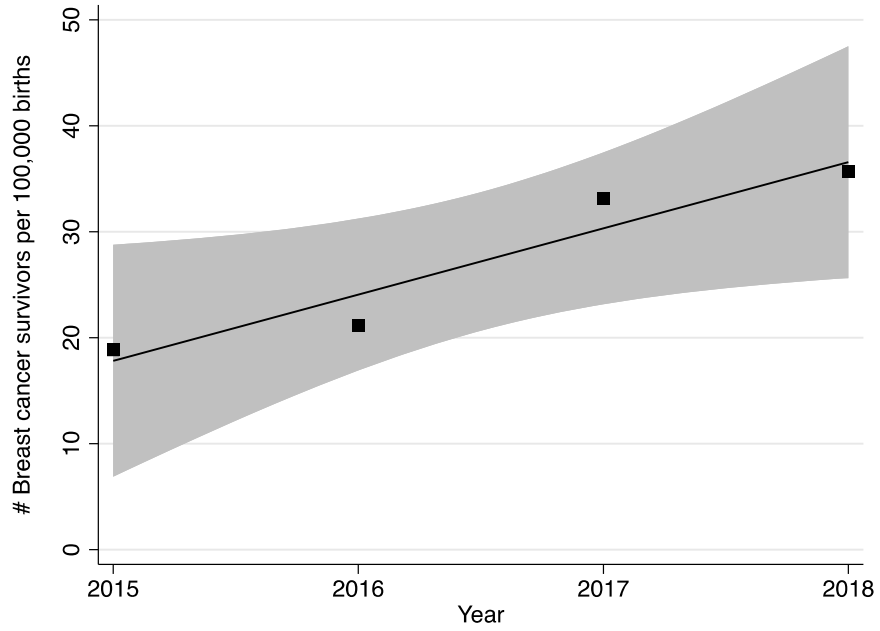

Fig. 1. Shows trends in the number of women who are BCSur at time of childbirth admission per 100,000 deliveries over the study years.

associated with an increased risk on multivariate analysis.

4. Discussion

Herein we present the results of a large population-based study of 2,103,216 birth related admissions evaluating major obstetric and maternal complications amongst 617 (0.03%) breast cancer survivors. Of note there was a trend of increasing numbers of BCSur per 100,000 births between 2015 and 2018. Similar findings were noted for each ethnic group. Women in the BCSur group were significantly older compared to non-BCSur population (34 vs. 28 years) and were more likely to suffer from preexisting chronic diseases including cardiopulmonary disease and diabetes mellitus at time of delivery. Additionally, higher rates of multiple gestation and obstetric or maternal events including non-reassuring fetal distress, preterm labor, and cesarean section and maternal infection were all more in the BCSur group. Nevertheless, the absolute number of fetal deaths was significantly lower in the BCSur group compared to the non-BCSur.

BCSsur who desire pregnancy face multiple challenges: older age, side effects of anti-cancer treatments including gonadotoxic effects, and an increased incidence of chronic medical conditions. This might explain why the pregnancy rates among BCSur are low compared to

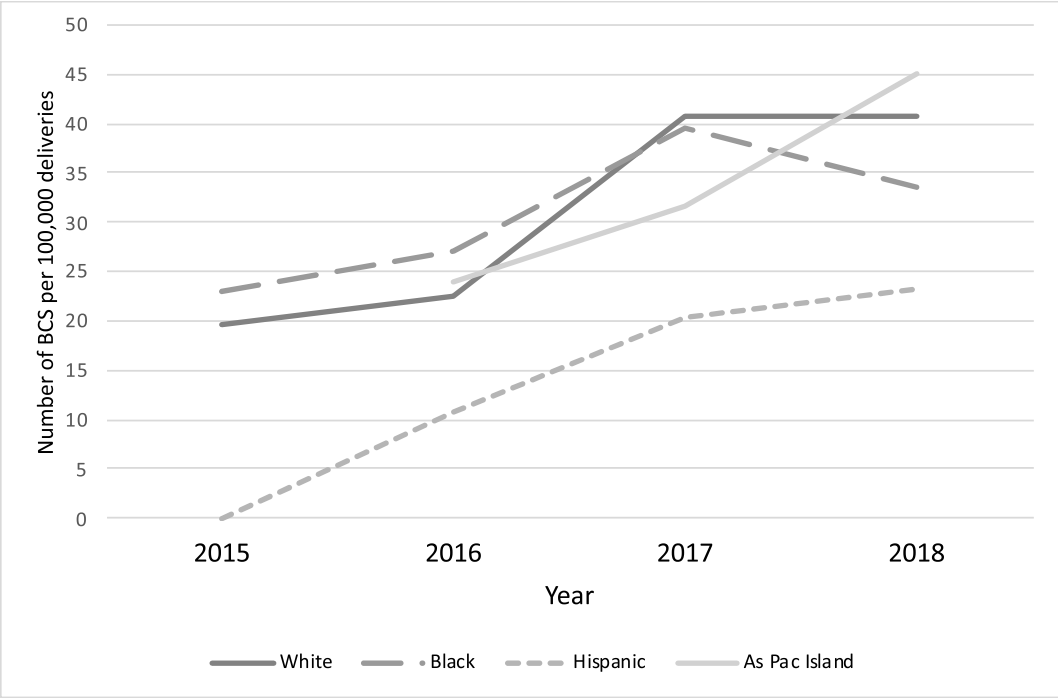

Fig. 2. Shows trends in the number of women who are BCSur at time of childbirth admission per 100,000 deliveries over the study years per ethnic group.

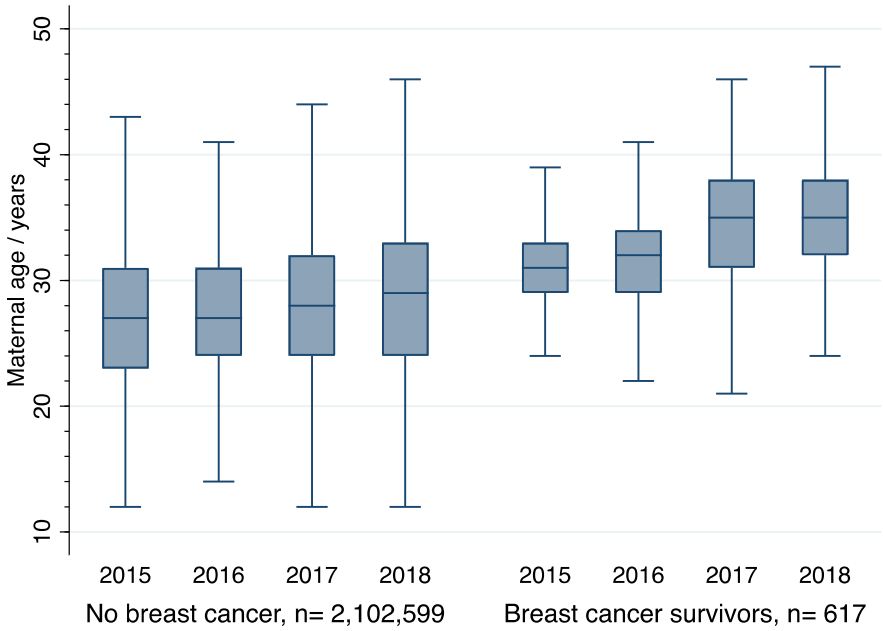

Fig. 3. The median age and standard deviation during the study years in the non-BCSur and BCSur group.

survivors of other cancer types [22]. If pregnancy is achieved, BCSsur are subjected to more obstetric and perinatal adverse outcomes [14,23].

Overall our results are aligned with a recent systematic review by D'Ambrosio et al. [14], summarizing obstetric outcomes from four studies with a total of 1466 BCSur patients compared to 6,912,485 control singleton pregnancies without breast cancer [14,24–28]. The BCSur group had statistically significant more preterm births (10% versus 6.8%), fetal distress (26.9% versus 22%%), and cesarean sections (38% versus 29%) compared with non-breast cancer survivors. Our finding of increased pre-existing chronic maternal comorbidities amongst BCSur may partially explain the increased incidence of obstetric complications seen in this population.

Disturbingly, in our study the BCSur group were more likely to have high social-economic group and more private health insurance compared to the population without a history of breast cancer. This issue should not be overlooked. An incidence of *2.75 times more multiple gestations* in the BCSur group, and the relationship between multiple gestations and advanced maternal age might imply that this is a result of fertility treatments (most probably following fertility preservation procedures at time of breast cancer diagnosis) in the BCSur population; such

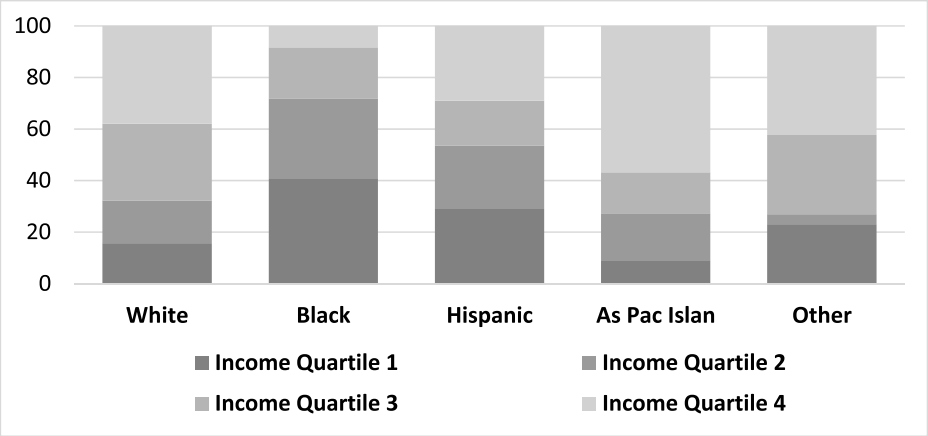

Fig. 4. Shows the household income for patient ZIP Code amongst BCSur according to the ethnic group. Category 1 is the lowest socioeconomic state (darkest gray), the border between the second and third categories is approximately the national median household income, and category 4 is above the median household income (lightest gray).

Table 2
Chronic diseases present at time of childbirth.

	Total, n = 2,103,216	Non-BCSur group, n = 2,102,599	BCSur, n = 617	OR	[95% CI]	p value
Cardiac disease	15,497	15,485 (0.74%)	12 (1.94%)	2.67	1.51–4.47	**<0.001**
Pulmonary disease	101,583	101,524 (4.8%)	59 (9.5%)	2.08	1.59–2.73	**<0.001**
Diabetes mellitus	18,853	18,842 (0.9%)	11 (1.8%)	2.01	1.11–3.64	**0.019**
Thyroid disease	76,941	76,894 (3.6%)	47 (7.6%)	2.17	1.61–2.93	**<0.001**
Anemia	290,174	290,067 (13.8%)	107 (17.3%)	1.31	1.06–1.62	**0.011**
Drug, alcohol or tobacco use	139,237	139,199 (6.6%)	38 (6.1%)	0.93	0.67–1.29	0.645

OR- odds ratio, OR > 1, indicates that the condition was overly-represented amongst the women with a personal history of breast cancer.CI- confidence interval; BCSur- breast cancer survivor. ICD codes defining each category are listed in the supplement. P- value of statistically significant results is in bold font.

Table 3
Obstetric and maternal events at time of childbirth.

	Total, n = 2,103,216	Non-BCSur group, n = 2,102,599	BCSur, n = 617	OR	95%CI	p value
Obstetric events						
Cesarean section	617,727	617,490 (29%)	237 (38%)	1.5	1.3–1.7	**<0.001**
Eclampsia	203,912	203,850 (9.7%)	62 10%)	1	0.8	0.767
Preterm labor	143,372	143,310 (6.8%)	62 (10%)	1.5	1.2–2	**0.001**
Fetal distress	461,014	460,850 (22%)	164 (26.6%)	1.3	1–1.5	**0.005**
Hemorrhage	75,287	75,264 (3.6%)	23 (3.7%)	1	0.7	0.843
Poor fetal growth	69,375	69,350 (3.3%)	25 (4%)	1.2	0.8–1.8	0.295
Fetal death	10,555	10,555 (0.5%)	0	[a]	[a]	0.078
Other fetal complications	28,215	28,201 (1.3%)	14 (2.3%)	1.7	1–2.9	**0.045**
Maternal events						
Maternal infection	149,198	149,135 (7%)	63 (10.2%)	1.490	1.148	**0.003**

OR- odds ratio, OR > 1, indicates that the condition was overly-represented amongst the women with a personal history of breast cancer. CI- confidence interval; BCSur- breast cancer survivor. ICD codes defining each category are listed in the supplement. P- value of statistically significant results is in bold font.
[a] Cannot be calculated due to no events in BCSur group.

procedures may not be accessible to all ethnic/socioeconomic groups. The mean household income for patients' ZIP Code was highest in Asian/Pacific Islander and white, and lowest in the black population. Low social-economic group, Medicaid or no insurance were associated with a higher incidence of complications. We also found a significantly negative correlation between Hispanic origin and the likelihood of being

Table 4
Univariate and multivariant analysis for demographic and baseline characteristics associated with occurrence of an adverse obstetric events.

Covariate	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age and Race						
Age (years)*	1.020	1.020–1.021	<0.001	1.023	1.023–1.024	<0.001
White	comparator				comparator	
Black	1.38	1.37–1.40	<0.001	1.35	1.34–1.36	<0.001
Hispanic	1.02	1.02–1.03	<0.001	1.06	1.06–1.07	<0.001
Asian/Pacific Islander	1.11	1.09–1.12	<0.001	1.09	1.07–1.10	<0.001
Other ethnicity	1.07	1.05–1.08	<0.001	1.07	1.06–1.09	<0.001
Medical cost coverage						
	comparator			comparator		
private	0.98	0.98–0.99	<0.001	1.01	1.01–1.02	<0.001
self/no charge	0.86	0.85–0.88	<0.001	0.87	0.85–0.88	<0.001
other	0.88	0.86–0.89	<0.001	0.92	0.90–0.94	<0.001
Median household income for patient's ZIP Code	0.988	0.985–0.990	<0.001	0.99	0.988–0.993	<0.001
Chronic diseases						
Diabetes mellitus	3.61	3.48–3.75	<0.001	3.22	3.10–3.37	<0.001
Cardiac disease	2.10	2.02–2.17	<0.001	1.80	1.74–1.87	<0.001
Lung disease	1.45	1.43–1.47	<0.001	1.34	1.33–1.36	<0.001
Thyroid disease	1.34	1.32–1.36	<0.001	1.24	1.22–1.26	<0.001
Anaemia	1.85	1.83–1.86	<0.001	1.76	1.74–1.77	<0.001
Drug/tobacco/alcohol use	1.31	1.29–1.32	<0.001	1.32	1.30–1.33	<0.001
Multiple gestations	9.02	8.68–9.38	<0.001	8.41	8.08–8.76	<0.001
Breast cancer diagnosis and treatment						
History of breast cancer	1.57	1.33–1.85	<0.001	1.24	1.02–1.50	0.03
History of radiation therapy	2.42	1.29–4.51	0.006	1.31	0.61–2.79	0.5
History of chemotherapy	2.53	1.57–4.09	<0.001	1.42	0.79–2.56	0.2

This table refers to the associations with any 'obstetric event' – a composite indicator variable representing the presence of any one or more of the following: poor intrauterine growth, fetal malposition, fetal distress, eclampsia (including pre-eclampsia and gestational associated hypertension), maternal exhaustion, cesarean section, preterm labor, hemorrhage, other fetal problems, operative vaginal delivery, abruption, and fetal death.
OR- odds ratio, OR > 1, indicates that the characteristic or condition was associated with the occurrence of an adverse obstetric event.
CI- confidence interval; BCSur- breast cancer survivor. *Older age. ICD codes defining each category are listed in the supplement.

Table 5
Univariate and multivariant analysis for maternal complications at time of childbirth.

Covariate	Univariate				Multivariate	
	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.99	0.98–0.99	**<0.001**	0.993	0.992–0.994	**<0.001**
Race						
White	comparator			comparator		
Black	1.79	1.77–1.82	**<0.001**	1.61	1.59–1.63	**<0.001**
Hispanic	1.12	1.10–1.14	**<0.001**	1.14	1.12–1.157	**<0.001**
Asian/Pacific Islander	1.34	1.31–1.36	**<0.001**	1.50	1.46–1.53	**<0.001**
Other ethnicity	1.21	1.18–1.24	**<0.001**	1.22	1.19–1.25	**<0.001**
Medical costs coverage						
Medicare/Medicaid	comparator		comparator			
private	0.71	0.70–0.72	**<0.001**	0.87	0.86–0.89	**<0.001**
self/no charge	0.67	0.65–0.70	**<0.001**	0.77	0.74–0.80	**<0.001**
other	0.74	0.72–0.77	**<0.001**	0.88	0.85–0.91	**<0.001**
Median annual household income quartile for patient's ZIP Code						
Median household income for patient's ZIP Code	0.920	0.915–0.924	**<0.001**	1.003	0.998–1.008	0.28
Pulmonary disease	1.75	1.71–1.78	**<0.001**	1.49	1.46–1.52	**<0.001**
Cardiac disease	3.23	3.10–3.35	**<0.001**	2.82	2.71–2.94	**<0.001**
Thyroid disease	1.06	1.03–1.09	**<0.001**	1.14	1.11–1.17	**<0.001**
Anaemia	1.79	1.77–1.8	**<0.001**	1.60	1.58–1.62	**<0.001**
Diabetes	1.73	1.66–1.81	**<0.001**	1.52	1.46–1.60	**<0.001**
Multiple gestations	1.18	1.13–1.22	**<0.001**	1.09	1.04–1.13	**<0.001**
Drug/tobacco/alcohol use	2.25	2.22–2.29	**<0.001**	2.13	2.09–2.16	**<0.001**
History of breast cancer	1.50	1.17–1.93	**0.001**	1.47	1.10–1.95	**0.008**
History of radiation therapy	2.44	1.19–4.99	**0.015**	2.04	0.83–5.02	0.12
History of chemotherapy	1.77	0.96–3.24	0.066	0.80	0.36–1.78	0.58

This table refers to the associations with any 'maternal complications – a composite indicator variable representing the presence of any one or more of the following acute maternal medical events: infections, renal events, cardiac events, respiratory events or vascular events.
OR- odds ratio, OR > 1, indicates that the characteristic or condition was associated with the occurrence of an adverse maternal complication at time of childbirth.
CI- confidence interval; BCSur- breast cancer survivor. ICD codes defining each category are listed in the supplement. P- value of statistically significant results is in bold font.

a breast cancer survivor at time of childbirth, while other ethnic groups had similar chances of being a BCSur. These differences could be due to medical and non-medical issues such as marital status, lack of social support, patient's or physician perceptions and believes, and unequal access to medical services [29].

The impact of racial, ethnic, and socioeconomic status on breast

cancer outcomes are well described [30]. In recent years the U.S. has witnessed decreased breast cancer mortality rates in the white population, thanks to an increased emphasis on screening programs/early detection, and more effective treatments. Unfortunately these dynamics have not been seen in all populations – even though black and Hispanic women have a lower incidence of breast cancer than white women, they tend to be younger at time of diagnosis, and have a higher breast cancer mortality rate [31–33]. Black women were also found to be at risk for early recurrence of triple negative breast cancer, possibly associated with social-economic group and poor health coverage [33].

Unlike many countries, such as Canada and most of the countries within Europe, with universal health care, the U.S. has a mixture of private and two kinds of government-track programs Medicare and Medicaid, which are specifically designed for elderly, people with disabilities, and low-income families. Others need to obtain private plans, either through their employer or on their own, which is often expensive and at times limited and requiring complimentary expensive self-payments. However even in Europe, access to health care for underprivileged BCSur can be problematic due to improper reimbursement, funding rules and regulations, as highlighted in the 12th European Breast Cancer Conference (EBCC) manifesto [34]. Likely, there are also disparities in BCSur maternal and neonatal care among European countries.

This study raises important considerations concerning the management of younger breast cancer patients in their reproductive years who are planning a family. Breast cancer is the most frequent malignancy arising in women of reproductive age, occurring in 1 in 68 women before the age of 40 and 1 in 220 before the age of 30 years [9]. Early detection, improvements in systemic therapy and other aspects of management, have resulted in excellent survival rates [35]. It has been estimated that the number of breast cancer survivors in the general population will increase by 22% between 2019 and 2030 (3.8 vs 4.9 million, respectively) [36]. Current recommendations are that women treated for breast cancer and who wish to have a child should be counselled that pregnancy is possible, as data suggest that pregnancy does not to compromise disease outcome, including in hormone receptors positive disease [9,15,35,37,38]. Of course, pregnancy should be planned not to disturb or delay critical anti-cancer therapy. As most breast cancer recurrences occur within the first three to five years after initial diagnosis (depending on the stage and molecular type of disease), patients are often advised to postpone pregnancy a few years after completion of therapy to increase the likelihood that there is no recurrence [13,19,37].

Further research is ongoing like the POSITIVE trial [NCT02308085] to evaluate the safety of endocrine therapy interruption in young breast cancer patients ($\leq$42 years) with estrogen positive tumors who wish to become pregnant. The results of our study, relying on a large database from the U.S., show similar outcomes of obstetric complications among BCSur to those reported in European countries [14,24–27] Further prospective studies are required to confirm these findings, and to evaluate appropriate interventions/surveillance during pregnancy to improve obstetrical outcomes in this population.

Our study has several limitations: As a study based on a large database it is dependent on correct ICD-10CM coding. The ICD-10CM breast cancer survivor code was adopted in late 2015, thus results presented in Figs. 1 and 2 could be possibly be related to increasing familiarity with the new code, however they are in line with the increasing numbers of women in the community who are breast cancer survivors [36] rather than reflecting an increase in the number of deliveries among BCSur. Precise definitions are not provided for ICD-10CM codes referring to obstetric events, such as 'preterm labor', 'fetal distress' and eclampsia. Furthermore, ICD-10CM coding for the conditions evaluated in the study, such as comorbidities, breast cancer history, obstetric and maternal complications might relate to transient events (e.g., cardiac dysfunction due to anthracyclines) that might not be relevant for the outcomes evaluated in our study. Our database did not include known risk factors for obstetric complications, which could not therefore be considered - including medically assisted procreation, previous obstetric complications and a history of sexually transmitted infections. Regarding breast cancer itself, the database did not detail the time period between the oncological diagnosis, cancer treatments and delivery. In addition, we were unable to evaluate the impact of various systemic therapies (e.g., anthracyclines, alkylating agents, taxane-based regimens and/or endocrine therapy) on outcome. Our methodology to exclude women transferred after delivery to another medical center was adopted in order to avoid the double-counting of cases, but may also have led to an underestimation of complications. Despite the size of the database, there only 617 deliveries amongst the BCSur; however, since no *a priori* power estimation sample size estimation was performed, some of the results may be statistically significant but have limited clinical significance. Finally, our dataset was gathered entirely in the U.S; it is unclear how generalizability our findings are to other countries, especially those with a universal health care or those with underdeveloped regions, where the practice of both obstetric and oncological health care may differ significantly. However, the need for team education of potential risks that may lead to complications is recommended to all.

Chemotherapy or radiation therapy were not associated on multivariant analysis with increased obstetric or maternal complications. Importantly, our findings are of particular interest as previous studies that reported obstetric complications amongst BCSur did not address the issue of maternal comorbidities and complications. Therefore, our results imply that this population needs to be assessed for pre-existing comorbidities that are not commonly associated with the age of this population – presumably related to their previous anti-neoplastic therapies [39].

5. Conclusions

As shown by our study, and reported by others, even though breast cancer survivors are at increased risk of obstetric and maternal complications, the absolute numbers are low. We advise that the care of all young patients with breast cancer should be discussed within a multidisciplinary team before any treatment decision, including consultation about fertility and family planning. When pregnancy is desired or planned, appropriate screening and management of potential comorbidities is needed, and the pregnancy should be managed by a multidisciplinary team. The use of the consultancy option such as the professional website ABCIP (Advisory Board on Cancer, Infertility and Pregnancy, composed of an international multidisciplinary expert team, available at https://www.ab-cip.org/ask-for-advice) for such cases should be considered.

As health providers, we should aim to allow this population, regardless of their ethnicity, to experience life to the fullest and by birth of offspring if they wish. It is our duty to assure the safety and quality of life, for both the parents and their children.

Contribution to authorship

OKP & YL -Acquisition, analysis. Interpretation of data- All, Drafting of manuscript- OKP; Revisions- All.

Details of ethics approval

The NIS is a publicly evaluable anonymized database, no ethics approval is required. An HCUP Data Use Agreement form was signed.

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Declaration of competing interest

None of the authors have relevant interests to disclose. Philip Poortmans is medical advisor of Sordine IORT Technologies, S.p.A., not related to the subject of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.02.008.

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