Published in final edited form as:

Am J Surg. 2018 October ; 216(4): 809–812. doi:10.1016/j.amjsurg.2018.07.060.

Characteristics and Diagnosis of Pregnancy and Lactation Associated Breast Cancer: Analysis of a Self-Reported Regional Registry

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Abstract

Background: Pregnancy-associated breast cancer (PABC) is the most common malignancy in pregnancy. However due to its infrequent occurrence, PABC continues to be poorly understood.

Methods: We performed a retrospective study using self-reported data from 1079 eligible women in a regional breast cancer registry.

Results: The PABC cases were more likely than non-PABCs to be younger than age 35 and have nodal involvement at diagnosis. Despite diagnosis at a young age, there was not an association between PABC and family history. For method of diagnosis, PABC was found on self-exam, while non-PABCs were found on mammography.

Conclusion: In conclusion, PABC is rarely detected by mammography and diagnosis is highly dependent on detection during self-breast exam. Women who are or recently were pregnant should be encouraged to perform regular self-breast exams to report any changes for further evaluation. Patient and clinician education regarding risk and realities of PABC is essential.

Introduction

Breast cancer is the most common malignancy, excluding non-melanoma skin cancers, in women in the United States as well as the most common malignancy associated with pregnancy.^{1, 2} The effects of pregnancy on the development of breast cancer are complex and poorly understood, however it is predicted that the incidence of pregnancy-associated breast cancer (PABC) will increase as woman delay childbirth to later in life.³ Therefore, it is important to develop a deeper understanding of the factors associated with PABC.

Pregnancy appears to have “dual effects” on the development of breast cancer resulting in an increase in risk during the first several years after pregnancy followed by a long-term protective effect for women who are younger than 35 at first delivery.^{2, 4, 5} Frequently,

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PABC is defined as diagnosis of breast cancer during or within one year of pregnancy/lactation.^{3, 6–9} However, there is movement to expand this definition to include those breast cancers diagnosed within five or possibly up to fifteen years after birth.^{10–12} Using a self-reported regional breast cancer registry, we had the unique opportunity to explore the characteristics of two populations of women with PABC: 1) those identified during or within one year of pregnancy/lactation and 2) those diagnosed within one to five years of pregnancy.

Methods

As PABC cases continue to increase, it is important to characterize the development and improve the ability to diagnose this disease process. We utilized two data sets involving members of the Breast Cancer Registry of Greater Cincinnati from 2004–2016. Information was self-reported by participants enrolled after diagnosis with updates collected periodically via questionnaires. Women diagnosed with breast cancer before age 45 were included in this study. Exclusion criteria for this analysis included male breast cancer, women diagnosed with breast cancer older than 45 years of age, and records missing information on age at time of diagnosis or association with pregnancy (Figure 1). The original analysis was based on information from the enrollment questionnaire, which defined PABC as diagnosis of breast cancer during or within one year of pregnancy/lactation (PABC-I). In 2016, a follow-up questionnaire was administered which asked if breast cancer diagnosis occurred between 1 and 5 years of pregnancy. A second analysis was completed using this definition of PABC (designated PABC-II). As shown in Figure 2, both analyses compared PABC-I or PABC-II cases to cases diagnosed in women less than 45 years old who had not experienced recent pregnancy (non-PABC). Women were asked about characteristics including tumor histology (ductal and/or lobular breast cancer) and hormone receptor status (estrogen and/or progesterone receptor positivity).

SAS Version 9.3 was used for analysis of data. Descriptive statistics related to demographic and clinical characteristics were calculated. For each categorical characteristic, difference in proportions was tested using the Chi-square test or Fisher's exact test. Differences in continuous variables were evaluated using t-tests. Multiple variable logistic regression analyses were conducted using forward and fitting of independent variables that modeled the probability of being a PABC-I case compared to non-PABC. Independent variables included age at diagnosis modeled as a dichotomous variable (< or > 35 years), method of diagnosis modeled as a three level categorical (self-breast exam, mammogram or other method), estrogen receptor positive breast cancer modeled as a three level categorical variable (yes, unknown, no), and nodal involvement at diagnosis (yes, unknown, no). Terms were retained in the model if the added variable was significant or caused a 15% change in beta estimate of other variables in the model. We calculated odds ratios (OR) and 95% confidence intervals (CI).

Results

PABC-I

Our PABC-I study sample included 1079 women diagnosed with breast cancer prior to age 45. Of these women, 5.8% met criteria for PABC-I (n=65) compared to 94.2% who did not meet PABC-I criteria (n=1014). Other studies have cited similar PABC rates ranging from 2.6% to 6.9% of breast cancer cases in women younger than 45 years of age.⁵ Thus, our population has an incidence similar to that previously described in the general population.

As seen in Table 1, we did not detect significant differences in race, tobacco or alcohol use, location of breast cancer, or tumor histology between PABC-I and non-PABC-I cases. In breast cancer literature, the reported average age of women diagnosed with PABC varies from 32 to 38.^{3,8} Similarly, we found that PABC-I cases were more likely than non-PABC-I comparisons to be younger than 35 years old at time of diagnosis (49.2% vs 14.8%, $p<0.01$). The mean age of those with PABC-I was 34.9 ± 4.7 years compared to 39.6 ± 4.5 years for those who had non-PABC-I. Nodal involvement at time of diagnosis was observed in 57.4% of PABC-I cases compared to 41.8% of non-PABC-I ($p=0.02$). Additionally, PABC-I cases were less likely to report that their tumor was estrogen receptor positive. We also noted there was not a difference in family history of breast cancer (first or second-degree relative) in those with PABC-I in comparison with non-PABC-I. Although most characteristics were found to be similar between PABC-I and non-PABC-I, PABC-I cases were diagnosed in younger women and were more likely to have nodal involvement at time of diagnosis. We also found that PABC-I cases were more often reported to have been found on self-breast exam compared to non-PABC-I cases (76.2% vs. 57.0%, $p<0.01$).

To further explore the determinants of PABC-I, we constructed several multivariable logistic regression models (Table 2). Our “full model” included 4 categorical predictors which were significant in the bivariate analyses: age at diagnosis, method of diagnosis, nodal involvement, and estrogen receptor positivity. In our “final model”, variables were retained if their addition of the variable was significant or caused a 15% change in the beta estimate of at least one other variable in the model. The significant predictors were age < 35 years at diagnosis (OR = 4.49, 95% CI, 2.65–7.62) and diagnosis by routine mammogram (OR = 0.15, 95% CI 0.03–0.71).

PABC-II

The increased risk of breast cancer associated with pregnancy may extend to 5 years and possibly 15 years or longer.^{2,4} Therefore, in our second analysis, we evaluated patients diagnosed with breast cancer 1 to 5 years postpartum (PABC-II). More detailed information, in response to questions on an update questionnaire, was received from 307 patients. Of these, 16.0% (n=49) met criteria for being diagnosed with PABC-II compared to 84.0% (n=258) who did not meet this criteria and were designated non-PABC-II (n=258). The characteristics of these two groups are listed in Table 3. We again noted a significant difference in age at diagnosis. However, there was no difference between these groups in terms of nodal involvement. The pathophysiology behind the differences in nodal involvement is unknown, but may have to do with the dramatic hormonal shifts during and

after pregnancy.⁵ As with the PABC-I group, there is a significant difference observed in the method of diagnosis. We again found PABC-II cases were more likely diagnosed by self-breast exam compared to non-PABC-II cases (73.5% vs. 51.6%, $p<0.01$), whereas non-PABC-II cases were more likely found by mammography compared to PABC-II (31.0% vs. 14.3%, $p<0.01$).

Discussion

It has been reported that delay in diagnosis of PABC ranges from 1 month up to 13 months.⁵ Only a third of PABC cases are diagnosed during pregnancy with the remaining diagnosed postpartum.^{5,13} We were unable to determine if this was the case in our cohorts as this data was not collected. However, the data does demonstrate the change in utility of diagnostic methods. Delay in diagnosis is likely due to signs of breast cancer mistaken by the patient and clinician as normal changes of the breast during pregnancy and lactation.^{5,14} In addition, physiologic changes of the breast make radiographic evaluation difficult.¹⁵ Many guidelines no longer recommend routine screening self- and clinical breast exams due to lack of evidence-based benefit.¹⁶ However, most women who are diagnosed with PABC have not yet met the recommended age threshold for routine screening mammography. In addition, the sensitivity of mammography is limited by the physiologic changes that occur in the breasts during pregnancy.¹⁵ Our data reinforces the importance of educating pregnant women and their clinicians on the risk of PABC as well as stressing the use of self- and clinical breast exams with prompt imaging and/or biopsy evaluation of suspicious changes during and following pregnancy.

The effect of family history on risk of PABC remains unclear. This may be due to the varying definitions of PABC or to differences in inclusion of certain relatives. Although we found no evidence of any association, Hou et al. found a correlation between a positive family history and PABC. However, they defined PABC as diagnosed during or within two years of pregnancy and the population was Nigerian.¹⁷ Similar to our results, Johansson et al. found that there was not an association between family history and breast cancer during or within 2 years of pregnancy and even up to 10 years post-partum.⁴ As women diagnosed with breast cancer at younger ages are more likely to have a family history of breast cancer, the absence of an association in those with PABC suggests some other causative factor, possibly hormonal. Until relationships are well understood and characterized, family history should be considered when assessing risk.

A potential limitation of this study is the accuracy of the data collected as it patient self-reported. Reporting by female patients and those with a higher education level have been associated with increased accuracy.¹⁸ All of our participants are women, however, their education level is unknown. In addition, the California Teacher Study provides validation regarding accuracy of self-reported cancers. Patients were more accurate reporting breast cancer diagnoses than others (sensitivity of 96.4%; specificity of 98.1%).¹⁹ Thus, we are confident that the data collected from our selected cohorts is reasonably accurate despite our inability to confirm self-reports with medical records for this data set.

Conclusions

In light of the ongoing and increasing incidence of PABC, it is important that we obtain a better understanding of this disease process and its temporal association with pregnancy as well as the impact of other factors including age and family history. The diagnosis of PABC is often delayed due to lack of symptom recognition by the patient/clinician and challenges in evaluation secondary to physiologic changes of the breast. PABC is rarely detected by mammography and diagnosis is highly dependent on detection during self-breast exam. Despite some screening guidelines not supporting self-breast exams, women who are or recently were pregnant should be encouraged to perform regular self-breast exams and self-breast awareness to report any changes for further evaluation. Patient and clinician education regarding risk and realities of PABC is essential.

Acknowledgements

We thank the members of the Breast Cancer Registry of Greater Cincinnati for providing the data used in these analyses and Victoria Straughn for outreach and data entry support.

Funding: This work was supported by the National Institutes of Health [grant numbers P30-ES006096, T32 GM063483].

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Highlights:

- Pregnancy-associated breast cancer (PABC) is the most common malignancy in pregnancy.
- PABC is diagnosed more often in young women and presents at a more advanced stage.
- PABC is rarely detected by mammography and highly dependent on self-breast exam.
- Women who are or recently were pregnant should practice breast self-awareness.
- Patient and clinician education regarding risk of PABC is essential.

Fig. 1.
Inclusion and exclusion criteria.

Fig. 2.
Defining PABC for analysis.

Table 1:

Characteristics of PABC-1 cases and comparison women

	PABC-I		non-PABC-I		
	N	(%)	N	(%)	P-value
Total women	65	(5.8%)	1014	(94.2%)	
Characteristics					
Age <35	32	(49.2%)	150	(14.8%)	<0.0001
Caucasian	61	(93.9%)	908	(89.6%)	0.3
African American	2	(3.1%)	64	(6.3%)	0.4 [†]
Tobacco Use	19	(29.2%)	380	(38.0%)	0.2
Alcohol Use	50	(76.9%)	734	(74.1%)	0.6
Breast Cancer Location					0.8 [†]
Right	32	(49.2%)	455	(45.0%)	
Left	32	(49.2%)	537	(53.1%)	
Both	1	(1.5%)	19	(1.8%)	
Histology					
Ductal	46	(70.8%)	685	(67.6%)	0.6
Lobular	1	(1.5%)	106	(10.5%)	0.02
Nodal Involvement	35	(57.4%)	399	(41.8%)	0.02
Receptors					
Estrogen Receptor Positive	33	(62.3%)	558	(73.9%)	0.06
Progesterone Receptor Positive	16	(39.0%)	240	(52.4%)	0.1
Family History	22	(33.9%)	313	(30.9%)	0.6
Detection of Breast Cancer					
Self-Exam	50	(76.2%)	578	(57.0%)	0.002
Mammography	4	(6.2%)	264	(26.0%)	0.0003 [‡]

Note: percentages are based on total women in each sample (N)

[†]Fishers exact test used. All other comparisons between categorical variables used Chi-square test to test for difference in proportions.

Table 2:

Multivariable logistic regression analysis of risk factors for PABC

		Model 1 – Full Model			Model 2 – Final Model		
	N	β	OR	95% CI	β	OR	95% CI
Age at Diagnosis							
Less than 35	182	0.74	4.40	2.58 – 7.49	0.75	4.49	2.65 – 7.62
Greater than 35	897	---	---	---	---	---	---
Method of Diagnosis							
Self-Exam	628	0.57	0.93	0.48 – 1.79	0.61	0.98	0.51 – 1.88
Routine Mammogram	259	-1.22	0.16	0.03 – 0.71	-1.24	0.15	0.03 – 0.70
Other method	192	---	---	---	---	---	---
Nodal Involvement							
Yes	434	0.30	1.63	0.94 – 2.83	0.28	1.53	0.89 – 2.63
Unknown	63	-0.11	1.08	0.35 – 3.34	-0.12	1.03	0.34 – 3.15
No	582	---	---	---	---	---	---
Estrogen Receptor Positive							
Yes	591	-0.07	0.66	0.36 – 1.21	---	---	---
Unknown	271	-0.28	0.53	0.25 – 1.15	---	---	---
No	217	---	---	---	---	---	---

Table 3:

Characteristics of PABC-2 cases and comparison women

	PABC-II		non-PABC-II		
	N	(%)	N	(%)	P-value
Total women	49	(16.0%)	258	(84.0%)	
Patient Characteristics					
Age <35	20	(40.8%)	25	(9.7%)	<0.0001
Caucasian	44	(89.8%)	244	(94.6%)	0.2 [†]
African American	5	(10.2%)	7	(2.7%)	0.03 [†]
Tobacco Use	14	(28.6%)	86	(33.9%)	0.5
Alcohol Use	35	(71.4%)	195	(77.4%)	0.4
Breast Cancer Location					0.3 [†]
Right	27	(56.3%)	116	(45.1%)	
Left	21	(43.8%)	133	(51.8%)	
Both	0	(0%)	8	(3.1%)	
Histology					
Ductal	39	(79.6%)	193	(74.8%)	0.5
Lobular	5	(10.2%)	26	(10.1%)	1.0 [†]
Nodal Involvement	17	(35.4%)	89	(35.7%)	1.0
Receptors					
Estrogen Receptor Positive	26	(63.4%)	155	(76.7%)	0.07
Progesterone Receptor Positive	10	(41.7%)	68	(52.7%)	0.3
Family History	11	(22.5%)	84	(32.6%)	0.2
Detection of Breast Cancer					
Self-Exam	36	(73.5%)	133	(51.6%)	0.005‡
Mammography	7	(14.3%)	80	(31.0%)	0.02‡

Note: percentages are based on total women in each sample(N)

[†]Fishers exact test used. All other comparisons between categorical variables used Chi-square test to test for difference in proportions.