Case Control Study of Women Treated With Chemotherapy for Breast Cancer During Pregnancy as Compared With Nonpregnant Patients With Breast Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Pregnancy • Breast cancer • Chemotherapy • Anthracycline • Survival

Learning Objectives

Discuss known data regarding outcomes in pregnancy-associated breast cancer.

Evaluate outcomes in a single institution when compared to nonpregnant breast cancer patients.

ABSTRACT

Background. The purpose of this analysis was to compare disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) between pregnant and nonpregnant patients with breast cancer.

Methods. From 1989 to 2009, 75 women were treated with chemotherapy during pregnancy. Each pregnant case was matched on age and cancer stage to two nonpregnant patients with breast cancer (controls). Fisher's exact test, the Kaplan-Meier method, and Cox proportional hazards regression models were used.

Results. Median follow-up time for patients who were alive at the end of follow-up ($n = 159$) was 4.20 years (range: 0.28–19.94 years). DFS at 5 years was 72% (95% confidence interval [CI]: 58.3%–82.1%) for pregnant patients and 57% (95% CI:

46.7%–65.8%) for controls ($p = .0115$). Five-year PFS was 70% (95% CI: 56.8%–80.3%) for pregnant patients and 59% (95% CI: 49.1%–67.5%) for controls ($p = .0252$). Five-year OS was 77% (95% CI: 63.9%–86.4%) for pregnant patients and 71% (95% CI: 61.1%–78.3%) for controls ($p = .0461$). Hazard ratio estimates favored improved survival for pregnant patients in univariate analyses and multivariate analyses, controlling for age, year of diagnosis, stage, and tumor grade.

Conclusions. For patients who received chemotherapy during pregnancy, survival was comparable to—if not better than—that of nonpregnant women. Pregnant patients with breast cancer should receive appropriate local and systemic therapy for breast cancer. *The Oncologist* 2013;18: 369–376

Implications for Practice: Women who are diagnosed during pregnancy should receive standard chemotherapy during pregnancy in the second and third trimester as part of multidisciplinary care with the medical oncologist, surgical oncologist, and obstetrician. For those women who receive standard therapy with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) chemotherapy during pregnancy and appropriate other biologic and endocrine therapies after delivery, outcomes similar to nonpregnant breast cancer patients can be expected.

INTRODUCTION

Women who are diagnosed with breast cancer during pregnancy have traditionally faced significant obstacles in their treatment for breast cancer. It has historically been described as a very rare occurrence, estimated in one case series at 13 cases per 100,000 live births [1]. Registries, however, do not account for unreported cases or pregnancies that were terminated at the time of diagnosis of breast cancer. In addition, the incidence of breast cancer diagnosed during pregnancy will also likely increase with the increasing trend of women delay-

ing childbearing into their 30s and even 40s with the help of reproductive technologies. Andersson et al. described an increase in the incidence of pregnancy-associated breast cancer, which they defined as breast cancer that is diagnosed during pregnancy or within 1 year postpartum, from 16 to 37.4 cases per 100,000 deliveries based on the Swedish National Health Registries from 1963 to 2002 [2].

Most of the available data on how to best manage breast cancer diagnosed during pregnancy come from case reports

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and retrospective series, because no randomized trial would be possible in this instance. Many of the older case series reported worse outcomes for women who were pregnant at the time of their diagnosis. This may be due to the fact that the women had delayed therapy, substandard therapy, or had no therapy. In many of these early reports, the timing and use of chemotherapy was sparsely described, if at all [3–5]. In some of the available case control studies that included both diagnosis during pregnancy and diagnosis within the 1 year after a pregnancy, women who received appropriate therapy were not found to have a worse outcome [6–8]. Additionally, there has been some evidence that women who are diagnosed with breast cancer within the 2 years after a pregnancy may have worse prognosis [9]. Therefore, separating the treatment of breast cancer diagnosed during pregnancy from those diagnosed after a pregnancy may be an important clinical distinction.

Since 1989 at The University of Texas M.D. Anderson Cancer Center, women who are diagnosed with breast cancer during pregnancy have been treated as part of a prospective trial approved by the institutional review board (IRB) [10, 11]. This study was the first prospective treatment trial of treating breast cancer during pregnancy. In this unique cohort, women were all treated with the same chemotherapeutic agents: 5-fluorouracil at 500 mg/m², doxorubicin at 50 mg/m², and cyclophosphamide at 500 mg/m² (FAC). The doxorubicin was infused over a 72-hour infusion in most cases. Other chemotherapies such as taxanes, biologic therapies such as trastuzumab, and endocrine therapies such as tamoxifen were given postpartum as per the standard of care at the time of the patient's diagnosis.

Although other case series have contributed to our knowledge of treatment for breast cancer during pregnancy, most of these patients were not treated uniformly with the same agents and the same schedules, with the exception of 20 patients treated with weekly epirubicin [12, 13]. The unique cohort of women described in this analysis was treated with the same chemotherapy in the second and third trimesters, and they were followed at a single institution. Thus, it is the ideal cohort to compare to nonpregnant patients with breast cancer treated at the same institution. The purpose of this analysis was to evaluate the disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) of women treated with chemotherapy during pregnancy when compared with age and stage-matched nonpregnant patients with breast cancer.

METHODS

From 1989 through 2009, 75 women were treated on an IRB-approved protocol with FAC chemotherapy during the second and third trimesters of pregnancy. Women were treated in a multidisciplinary fashion with fetal ultrasounds performed prior to dosing of chemotherapy. This protocol has been previously described [10, 11]. The median age of delivery was 37 weeks (range: 29–41 weeks) and each pregnancy resulted in a live birth. Under a separate IRB-approved protocol, women who were treated for breast cancer and were not pregnant (controls) were identified through our institutional tumor bank, as well as through the Breast Cancer Management System Database prospectively maintained by the Department of

Breast Medical Oncology at The University of Texas M.D. Anderson Cancer Center. Treatment for controls was not on a standard protocol; treatments used are outlined in Table 1. Anthracycline regimens used in addition to FAC for controls are also included. Surgical outcomes from this cohort have been previously described [14]. Other therapies, including taxanes, trastuzumab, and endocrine therapy, were given when clinically indicated as per standard of care of treatment at the time of diagnosis after delivery. No trastuzumab was given during pregnancy because of the known effects of oligo- and anhydramnios [15, 16]. Radiation, when appropriate, was not given until after delivery.

Pathological diagnosis was performed by a dedicated breast pathologist for both the pregnant and nonpregnant patients with breast cancer at the time of diagnosis. Pathological information was extracted from the medical record.

Statistical Analysis

Controls were matched to cases on a 2:1 ratio based on patient age at diagnosis (<35 years or 36–45 years), stage at diagnosis (stage I, II, III, or IV), and year of diagnosis (before 1997, 1997–2009). Control subjects were chosen to ensure that the frequency of each matching factor was the same as that found in the case group. The only exception was year of diagnosis, because we were missing five control candidates in the designated age group who were diagnosed before 1997. To select the five additional controls, we chose patients who were diagnosed in 1997 or later who did not have hormonal therapy and who allowed the sample to stay balanced on patient age at diagnosis and disease stage.

Study groups were compared using the Fisher's exact test for categorical variables and the Kruskal-Wallis test for ordinal variables. Overall survival was calculated from the date of diagnosis until the date of death or last follow-up visit among those alive at the end of the follow-up period. PFS was calculated from the time of diagnosis until the time of metastasis or, if no metastasis was recorded, time to last follow-up visit. We included PFS as an outcome because three of the patients received therapy but developed metastatic disease before completing definitive surgery. DFS was calculated from the time of surgery until the time of metastasis or, if no metastasis was recorded, time to last follow-up visit. Patients who had not progressed or died by last follow-up visit were censored.

Survival curves were constructed using the Kaplan-Meier product limit method and compared using the log-rank test. Cox proportional hazards regression analysis was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for demographic and clinical characteristics and treatment variables. Univariate models were fit to evaluate the predictive effect of each factor alone and then multivariate models were fit. Multivariate models included patient age, year of diagnosis, tumor stage, and tumor nuclear grade along with study cohort. All reported *p* values were two-sided, and *p* values less than .05 were considered statistically significant. Analyses were performed using SAS for Windows (release 9.2; SAS Institute, Cary, NC).

RESULTS

The demographic and clinical characteristics of pregnant patients and controls are shown in Table 1. Patient age at diagnosis for pregnant patients was 24–35 years for 53 patients

Table 1. Frequency distribution of patient, tumor, and treatment characteristics by study group and results of Fisher's exact test to compare study groups

Category	Variable	Pregnant patients		Nonpregnant patients		Total		p value
		n	%	n	%	n	%	
Age group for matching	30–35 yrs	36	48.00	66	44.00	102	45.33	.7734
	<30 yrs	17	22.67	40	26.67	57	25.33	
	>35 yrs	22	29.33	44	29.33	66	29.33	
Diagnosis year group for matching	Before 1997	22	29.33	39	26.00	61	27.11	.6346
	On or after 1997	53	70.67	111	74.00	164	72.89	
Patient race/ethnicity	White	51	68.00	89	60.14	140	62.78	.5691
	Hispanic	12	16.00	34	22.97	46	20.63	
	African American	10	13.33	18	12.16	28	12.56	
	Asian, Pacific Islander	2	2.67	7	4.73	9	4.04	
Histology	Lobular	1	1.33	2	1.34	3	1.34	1.0000
	Ductal	71	94.67	140	93.96	211	94.20	
	Mixed ductal and lobular	2	2.67	4	2.68	6	2.68	
	Other	1	1.33	3	2.01	4	1.79	
Clinical stage if neoadjuvant therapy	I	5	6.67	10	6.67	15	6.67	1.0000
	II	36	48.00	72	48.00	108	48.00	
Path stage if no neoadjuvant therapy	III	34	45.33	68	45.33	102	45.33	
Nuclear grade	I	0	0.00	9	6.00	9	4.00	.0521
	II	12	16.00	29	19.33	41	18.22	
	III	63	84.00	112	74.67	175	77.78	
Hormone receptor status (ER or PR positive)	Negative	31	51.67	59	43.07	90	45.69	.2804
	Positive	29	48.33	78	56.93	107	54.31	
HER2 status	Negative	43	72.88	72	68.57	115	70.12	.5983
	Positive	16	27.12	33	31.43	49	29.88	
Triple receptor status	HR– and Her2–	24	40.68	27	25.96	51	31.29	.2810
	HR+ and Her2–	19	32.20	44	42.31	63	38.65	
	HR– and Her2+	6	10.17	14	13.46	20	12.27	
	HR+ and Her2+	10	16.95	19	18.27	29	17.79	
Lymphatic invasion	Negative	29	69.05	62	50.00	91	54.82	.0477
	Positive	13	30.95	62	50.00	75	45.18	
Vascular invasion	Negative	30	71.43	63	54.31	93	58.86	.0674
	Positive	12	28.57	53	45.69	65	41.14	
Neoadjuvant chemotherapy	No	35	46.67	67	44.97	102	45.54	.8871
	Yes	40	53.33	82	55.03	122	54.46	
Neoadjuvant chemotherapy agents	Anthracycline	9	27.27	26	34.21	35	32.11	.0750
	Anthracycline + taxane	18	54.55	40	52.63	58	53.21	
	Anthracycline + taxane + trastuzumab	6	18.18	4	5.26	10	9.17	
	Other	0	0.00	6	7.89	6	5.50	
Response to neoadjuvant therapy	Progressive disease	0	0.00	10	15.38	10	11.36	.1592
	Stable disease	4	17.39	6	9.23	10	11.36	
	Partial response	16	69.57	41	63.08	57	64.77	
	Pathologic complete response	3	13.04	8	12.31	11	12.50	
Adjuvant chemotherapy	No	29	39.73	44	29.73	73	33.03	.1710
	Yes	44	60.27	104	70.27	148	66.97	

(continued)

Table 1. (Continued)

Category	Variable	Pregnant patients		Nonpregnant patients		Total		p value
		n	%	n	%	n	%	
Adjuvant chemotherapy: taxanes	No	28	70.00	44	42.31	72	50.00	.0049
	Yes	12	30.00	60	57.69	72	50.00	
Adjuvant chemotherapy: trastuzumab	No	35	87.50	84	80.77	119	82.64	.4628
	Yes	5	12.50	20	19.23	25	17.36	
Adjuvant hormone therapy	No	56	74.67	91	60.67	147	65.33	.0390
	Yes	19	25.33	59	39.33	78	34.67	
Surgical treatment	No	3	4.00	3	2.00	6	2.67	.4030
	Yes	72	96.00	147	98.00	219	97.33	
Definitive surgical procedure	Mastectomy	54	76.06	104	71.23	158	72.81	.7803
	Segmental mastectomy	16	22.54	40	27.40	56	25.81	
	Biopsy	1	1.41	2	1.37	3	1.38	
Adjuvant radiation therapy	No	23	30.67	59	39.33	82	36.44	.2113
	Yes	49	65.33	89	59.33	138	61.33	
	Unknown	3	4.00	2	1.33	5	2.22	
Lymph node surgery	Sentinel lymph node	29	40.85	63	42.86	92	42.20	.8838
	Axillary lymph node	42	59.15	84	57.14	126	57.80	

(70.67%) and 36–45 years for 22 patients (29.33%). Tumor stage at diagnosis among pregnant patients was stage I for 5 patients (6.67%), stage II for 36 patients (48.00%), and stage III for 34 patients (45.33%). Twenty-two pregnant patients (29%) were diagnosed before 1997.

We compared the demographic and clinical characteristics of pregnant patients with controls and found that lymphatic invasion was slightly lower in the pregnant (31%) versus nonpregnant patients (50%; $p = .048$). Adjuvant hormonal therapy appeared to be used less frequently in the pregnant patients (25%) than in the nonpregnant patients (39%; $p = .04$). Adjuvant taxane therapy was used in 30% of pregnant patients and 58% of nonpregnant patients ($p = .005$). In addition, there was a nonsignificant trend toward a higher percentage of grade 3 (vs. lower grade) disease in pregnant versus nonpregnant patients ($p = .052$).

Survival Estimates

Median follow-up among patients alive at the end of follow-up ($n = 159$) was 4.20 years (range: 0.28–19.94 years). DFS was significantly different by study group ($p = .012$). Median DFS, which was not attained for pregnant patients, was 6.21 years (95% CI: 4.62–18.84) for controls. One-year DFS was 88% for both pregnant patients (95% CI: 76.7%–93.6%) and controls (95% CI: 81.1%–92.2%), but 5-year DFS was 72% (95% CI: 58.3%–82.1%) for pregnant patients and 57% (95% CI: 46.7%–65.8%) for controls (Fig. 1A). PFS also differed significantly between the study groups ($p = .025$). Median PFS, which was not attained for pregnant patients, was 6.27 years (95% CI: 4.89–19.09 years) for controls. One-year PFS was 94% (95% CI: 85.5%–97.8%) for pregnant patients and 92% (95% CI: 86.4%–95.6%) for controls. Five-year PFS was 70% (95% CI: 56.8%–80.3%) for pregnant patients and 59% (95% CI: 49.1%–67.5%) for controls (Fig. 1B).

Of the 66 deaths observed, 65 were among those who had evidence of breast cancer; the cause of death for one patient was unknown. Median OS for the entire study group was 16.69 years (95% CI: 8.16 years; upper limit not attained). OS differed significantly for pregnant patients and controls ($p = .046$). Median OS, which was not attained for pregnant patients, was 8.39 years (95% CI: 6.58 years; upper limit not attained) for controls. One-year OS was 99% (95% CI: 90.7%–99.8%) for pregnant patients and 97% (95% CI: 91.9%–98.5%) for controls. Five-year survival was 77% (95% CI: 63.9%–86.4%) for pregnant patients and 71% (95% CI: 61.1%–78.3%) for controls (Fig. 1C).

Multivariate Models of Outcome

The variables considered as predictors for survival outcomes included study group, age at diagnosis, year of diagnosis, clinical cancer stage (stage III vs. I/II), and tumor nuclear grade (grade 3 vs. 1/2). For all three outcomes, study group and clinical cancer stage were significant predictors of survival in the multivariate models that also included patient age, year of diagnosis, and tumor grade (Table 2).

Disease-Free Survival

Taking into account the other variables in the model to predict DFS, nonpregnant patients had approximately a twofold increase in risk of progression compared with risk of those in the pregnant cohort (HR: 2.09, 95% CI: 1.19–3.67; $p = .011$); having stage III versus stage I or II cancer almost doubled risk of disease progression (odds ratio: 1.83, 95% CI: 1.16–2.91; $p = .01$).

Progression-Free Survival

In the multivariate model to predict PFS, patients in the nonpregnant cohort experienced a 90% increase in risk of progression

Figure 1. Survival estimates of pregnant versus nonpregnant breast cancer patients. **(A):** Disease-free survival. **(B):** Progression-free survival. **(C):** Overall survival.

Abbreviation: met, metastasis.

(HR: 1.90, 95% CI: 1.11–3.26; $p = .020$). Patients with stage III disease had a 77% increased risk compared with patients with lower-stage disease (HR: 1.77; 95% CI: 1.13–2.80; $p = .014$).

Overall Survival

The full model to predict OS indicated that patients in the non-pregnant cohort had an 87% increased risk of death (HR: 1.87, 95% CI: 1.04–3.36; $p = .037$). Patients with stage III disease had 2.2 times the risk of death compared with patients with lower-stage disease (HR: 2.20, 95% CI: 1.32–3.67; $p = .003$).

We also evaluated if estrogen receptor (ER) status influenced outcomes during pregnancy. Of the 225 patients included in this study, ER status was available for 201 patients. Ninety-eight patients (48.76%) were ER negative and 103 patients (51.24%) were ER positive. The 24 missing cases were diagnosed prior to endocrine therapy being routinely given to premenopausal patients. Figure 2 illustrates these findings with respect to ER status and overall survival.

DISCUSSION

We evaluated our cohort of women who were treated for breast cancer during pregnancy and compared them with women who were not pregnant at the time of their breast cancer diagnosis. This cohort is unique because women were assessed at a single institution, treatment plans were made at a

single institution, and all women who were pregnant received the same chemotherapy during pregnancy. Our data showed statistically significant improvements in DFS, PFS, and OS for women treated during pregnancy when compared with non-pregnant controls.

The findings of this study are reassuring and intriguing. Although the survival estimates show improved outcomes, given the number of patients evaluated in this analysis, we believe it is important evidence that pregnant women who seek and receive therapy during pregnancy at least have clinical outcomes that are no worse than nonpregnant patients with breast cancer. This study provides a very important finding that can be used when counseling patients on the risks from breast cancer diagnosed during pregnancy. Termination of pregnancy is still recommended by some clinicians to proceed with full and appropriate treatment of breast cancer. Although any individual situation may require specific interventions, our data, added to other evidence [12, 17–18], do not support termination as a necessary routine procedure. With the suggestion of better survival, it is intriguing to consider whether this finding is simply due to chance or other group differences, including an underlying biology changing the tumor or its response to systemic therapies—an area that is undergoing continued research. Preoperative therapy in these pa-

Table 2. Cox proportional hazards regression models to predict survival

				Univariate model				Multivariate model			
				Hazard ratio				Hazard ratio			
Variable	Level	Events	Total	HR	95% CI		<i>p</i> value	HR	95% CI		<i>p</i> value
Disease-free survival (77 events/217 total)											
Study group	Nonpregnant	60	145	2.00	1.16	3.45	.0131	2.09	1.19	3.67	.0106
	Pregnant	17	72	1.00				1.00			
Age at diagnosis (yrs)		77	217	0.99	0.95	1.03	.5106	0.99	0.95	1.03	.7277
Year of diagnosis		77	217	1.00	0.96	1.05	.8463	0.99	0.94	1.03	.6318
Clinical cancer stage	Stage III	43	93	1.99	1.27	3.12	.0027	1.83	1.16	2.91	.0098
	Stage II or I	34	124	1.00				1.00			
Nuclear grade	Grade 3	61	169	1.44	0.83	2.50	.1986	1.41	0.79	2.53	.2453
	Grade 2 or 1	16	48	1.00				1.00			
Progression-free survival (79 progressions/220 total)											
Study group	Nonpregnant	60	145	1.80	1.07	3.04	.0272	1.90	1.11	3.26	.0195
	Pregnant	19	75	1.00				1.00			
Age at diagnosis (yrs)		79	220	0.99	0.96	1.03	.7173	1.00	0.96	1.04	.9461
Year of diagnosis		79	220	1.00	0.96	1.04	.9343	0.98	0.94	1.03	.4782
Clinical cancer stage	Stage III	44	95	1.92	1.23	2.99	.0041	1.77	1.13	2.80	.0135
	Stage II or I	35	125	1.00				1.00			
Nuclear grade	Grade 3	63	172	1.47	0.85	2.55	.1724	1.46	0.81	2.60	.2046
	Grade 2 or 1	16	48	1.00				1.00			
Overall survival (66 deaths/225 total)											
Study group	Nonpregnant	50	150	1.77	1.00	3.12	.0490	1.87	1.04	3.36	.0365
	Pregnant	16	75	1.00				1.00			
Age at diagnosis (yrs)		66	225	0.98	0.94	1.03	.4836	0.99	0.95	1.04	.7135
Year of diagnosis		66	225	1.01	0.96	1.06	.6995	0.99	0.94	1.05	.7335
Clinical cancer stage	Stage III	42	98	2.45	1.48	4.05	.0005	2.20	1.31	3.67	.0026
	Stage II or I	24	127	1.00				1.00			
Nuclear grade	Grade 3	55	175	1.89	0.99	3.62	.0550	1.73	0.88	3.40	.1137
	Grade 2 or 1	11	50	1.00				1.00			

Abbreviations: CI, confidence interval; HR, hazard ratio.

tients with evaluation of the tumor and its residual disease may be fruitful in addressing this question. This research, in addition to the follow-up of the children who were exposed to chemotherapy in utero, is ongoing.

Azim et al. compared 65 pregnant patients with breast cancer with nonpregnant patients with cancer; they found results conflicting with our study, with a decrease in DFS after a median follow-up of 4 years [19]. Although overall patient characteristics were similar, a potential explanation for the difference in these findings may be in the treatment strategies. In the study by Azim et al., not all patients received chemotherapy and only one was reported to have received third-generation chemotherapy in totality. The authors noted that the pregnant patients most often received weekly epirubicin. The more aggressive chemotherapy strategies used in our cohort may potentially account for some of these observed differences.

In our study, it is not clear exactly why we observed improved outcomes in the pregnant patients. It may be due to the relatively small numbers of patients involved in this cohort, which is why we caution against using this study as definitive evidence that pregnant patients do decidedly better. The outcomes may also be influenced by the differing motivational factors of a pregnant patient seeking treatment in a tertiary care center. It is still unclear if the pregnancy itself may influence the response to therapy; the available data for this analysis do not allow us to directly investigate an underlying biological answer to this question. However, it is interesting to note that in related situations, such as fertility preservation, early estimates show trends to improved outcomes; in addition, there are mounting data regarding pregnancy after a diagnosis of breast cancer, even when the “healthy mother effect” is taken into account [20, 21]. Further investigation into these clinical situations may provide further insight into

Figure 2. Impact of hormone receptor status and overall survival in pregnant patients with breast cancer.

Abbreviations: ER, estrogen receptor; HR, hazard ratio; LCL, lower confidence limit; nonpreg, nonpregnant; UCL, upper confidence limit.

the role of higher levels of circulating hormones at the time of diagnosis and treatment of breast cancer.

This study did have several limitations. First, it is a retrospective cohort study; randomized level 1 evidence is not possible for this clinical situation. Patient selection was limited to those women who participated in the clinical trial evaluating chemotherapy during pregnancy; therefore, these patients may have different characteristics than other women seen in the institution who were not pregnant. Matching was also difficult. After excluding women who did not have a pregnancy in the year before they were diagnosed, finding appropriate controls was challenging. Breast cancer during pregnancy occurs in young women; given the incidence of breast cancer in women in their 20s and 30s, perfect matching was unobtainable. To match to the best of our ability, we needed to group some variables together, such as age at diagnosis, year of diagnosis, and stage. Because many of our patients received preoperative chemotherapy, we tried to match on clinical stage because we felt that matching for residual disease would be even more problematic. In addition, we used 1997 as a pivotal year in our analysis because it was the year that we started using tamoxifen routinely in premenopausal women who were not part of a clinical trial at our center. In five cases, we had significant difficulty matching because of age of diagnosis and year of diagnosis, so we had to look outside of the year of diagnosis.

There were also limitations in the variables that could be included in the multivariable models given the years that spanned these cases and the changes in treatment guidelines during these years. Although we saw group differences in lymphatic invasion, adjuvant hormonal therapy, and adjuvant taxane therapy, we were not able to include these variables in the multivariate models due to confounding or a high percentage of missing values. For example, we did not include histology in the survival modeling because it lacked variability (94% were ductal, 1% were lobular, 3% were mixed ductal and lobular, and 2% were other histology). Use of taxanes varied during the study period. Women with more advanced cancers (most notably, node-positive can-

cer) were likely to receive taxanes. After taxanes demonstrated benefit in randomized clinical trials, taxanes were added to treatment plans as standard of care. Thus, the use of taxanes can be seen as a surrogate marker for more aggressive tumors. Medical records were missing information on lymphatic invasion for 26% of observations and on hormone receptor status for 12% of observations. Both variables were more frequently missing among those diagnosed during the earlier years of the study period and for those in the pregnant cohort. These limitations in the potential predictors that could be considered for modeling resulted from changes in treatment guidelines during the span of the study.

Although this is likely the longest follow-up on a prospectively collected cohort that is continuing to grow, the numbers do limit the power of our conclusions. A longer follow-up period of this growing cohort in collaboration with other growing cohorts throughout the world is needed to continue to evaluate this population.

The treatment of breast cancer during pregnancy has evolved significantly over the past two decades. Information from this cohort has been important in changing the paradigm of treating pregnant patients with cancer [22]. Our data support the concept that treating women with systemic chemotherapy in the second and third trimesters in a multidisciplinary fashion can be done effectively without significantly worse outcomes for pregnant patients with breast cancer.

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REFERENCES

- Smith LH, Dalrymple JL, Leiserowitz GS et al. Obstetrical deliveries associated with maternal malignancy in California, 1992 through 1997. *Am J Obstet Gynecol* 2011;184:1504–1512.
- Andersson TM, Johansson AL, Hsieh CC et al. Increasing incidence of pregnancy-associated breast cancer in Sweden. *Obstet Gynecol* 2009;114:568–572.
- Ribeiro G, Jones DA, Jones M. Carcinoma of the breast associated with pregnancy. *Br J Surg* 1986;73:607–609.
- Tretli S, Kvalheim G, Thoresen S et al. Survival of breast cancer patients diagnosed during pregnancy or lactation. *Br J Cancer* 1988;58:382–384.
- Bonnier P, Romain S, Dilhuydy JM et al. Influence of pregnancy on the outcome of breast cancer: A case-control study. *Int J Cancer* 1997;72:720–727.
- Beadle BM, Woodward WA, Middleton LP et al. The impact of pregnancy on breast cancer outcomes in women ≤ 35 years. *Cancer* 2009;115:1174–1184.
- Murphy C, Mallam D, Stein S et al. Pathologic features and outcomes of pregnancy-associated breast cancer (PABC): A case control study. *J Clin Oncol* 2010;28:(suppl15):1589a.
- Stensheim H, Møller B, van Dijk T et al. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: A registry-based cohort study. *J Clin Oncol* 2009;27:45–51.
- Johansson AL, Andersson TM, Hsieh CC et al. Increased mortality in women with breast cancer detected during pregnancy and different periods postpartum. *Cancer Epidemiol Biomarkers Prev* 2011;20:1865–1872.
- Berry DL, Theriault RL, Holmes FA et al. Management of breast cancer during pregnancy using a standardized protocol. *J Clin Oncol* 1999;17:855–861.
- Hahn KM, Johnson PH, Gordon N et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. *Cancer* 2006;107:1219–1226.
- Cardonick E, Dougherty R, Grana G et al. Breast cancer during pregnancy: Maternal and fetal outcomes. *Cancer J* 2010;16:76–82.
- Peccatori FA, Azim HA Jr, Scarfone G et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). *Breast Cancer Res Treat* 2009;115:591–594.
- Dominici LS, Kuerer HM, Babiera G et al. Wound complications from surgery in pregnancy-associated breast cancer (PABC). *Breast Dis* 2010;31:1–5.
- Bader AA, Schlembach D, Tamussino KF et al. Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. *Lancet Oncol* 2007;8:79–81.
- Beale JM, Tuohy J, McDowell SJ. Herceptin (trastuzumab) therapy in a twin pregnancy with associated oligohydramnios. *Am J Obstet Gynecol* 2009;201:e13–e14.
- Nugent P, O'Connell TX. Breast cancer and pregnancy. *Arch Surg* 1985;120:1221–1224.
- Deemarsky L, Neishtadt E. Breast cancer and pregnancy. *Breast* 1981;7:17.
- Azim HA Jr, Botteri E, Renne G et al. The biological features and prognosis of breast cancer diagnosed during pregnancy: A case-control study. *Acta Oncol* 2012;51:653–661.
- Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: A prospective controlled study. *J Clin Oncol* 2008;26:2630–2635.
- Azim Jr HA, Santoro L, Pavlidis N et al. Safety of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies. *Eur J Cancer* 2011;47:74–83.
- Amant F, Deckers S, Van Calsteren K et al. Breast cancer in pregnancy: Recommendations of an international consensus meeting. *Eur J Cancer* 2010;46:3158–3168.

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