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ORIGINAL REPORT

Prognosis of Women With Primary Breast Cancer Diagnosed During Pregnancy: Results From an International Collaborative Study

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ABSTRACT

Purpose
We aimed to determine the prognosis of patients with breast cancer diagnosed during pregnancy (BCP).

Patients and Methods
In this cohort study, a multicentric registry of patients with BCP (from Cancer in Pregnancy, Leuven, Belgium, and GBG 29/BIG 02-03) compiled pro- and retrospectively between 2003 and 2011 was compared with patients who did not have associated pregnancies, using an age limit of 45 years. Patients with a diagnosis postpartum were excluded. The main analysis was performed using Cox proportional hazards regression of disease-free survival (DFS) and overall survival (OS) on exposure (pregnant or not), adjusting for age, stage, grade, hormone receptor status, human epidermal growth factor 2 status, histology, type of chemotherapy, use of trastuzumab, radiotherapy, and hormone therapy.

Results
The registry contained 447 women with BCP, mainly originating from Germany and Belgium, of whom 311 (69.6%) were eligible for analysis. The nonpregnant group consisted of 865 women. Median age was 33 years for the pregnant and 41 years for the nonpregnant patients. Median follow-up was 61 months. The hazard ratio of pregnancy was 1.34 (95% CI, 0.93 to 1.91; $P = .14$) for DFS and 1.19 (95% CI, 0.73 to 1.93; $P = .51$) for OS. Cox regression estimated that the 5-year DFS rate for pregnant patients would have increased from 65% to 71% if these patients had not been pregnant. Likewise, the 5-year OS rate would have increased from 78% to 81%.

Conclusion
The results show similar OS for patients diagnosed with BCP compared with nonpregnant patients. This information is important when patients are counseled and supports the option to start treatment with continuation of pregnancy.

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INTRODUCTION

Breast cancer is one of the most commonly encountered types of malignancy during pregnancy.[1,2] Approximately 0.2% to 2.6% of all breast cancers occur during pregnancy (BCP).[3,4] There was a general belief among physicians in the first half of the 20th century that breast cancer, under the stimulus of pregnancy, was especially aggressive,[5] and surgical treatment was pointless and thus contraindicated.[6] Indeed, the gestational physiologic alterations in the breast result in later diagnosis and higher-stage tumors. A comprehensive review from 1953 showed improved survival rates for patients with breast cancer in association with pregnancy, from 0% 10-year survival before 1920 to 22.4% in the period from 1941 to 1950.[7] The survival rates were poorer than in the nonpregnant patients, probably because of the advanced stage of disease and delay in treatment; prompt commencement of treatment was necessary to improve survival rates. Since then, surgical treatment of BCP has become commonplace, and in the last decade, chemotherapeutic treatment during the second and third trimesters of pregnancy has also been introduced and deemed unharmful to the fetus.[8-10]

Whether pregnancy itself negatively influences prognosis remains a subject of debate. We still have no comprehensive understanding of the interaction between pregnancy and breast cancer carcinogenesis. Some studies have shown a poorer prognosis for BCP,[11-16] whereas others have found similar survival rates when compared with a control group of nonpregnant patients.[17-23] Up to now, reports on prognosis have had two major limitations, including small cohorts and the pooling of breast cancer diagnosed during and within 1 year after pregnancy (ie, pregnancy-associated breast cancer).

The aim of this study was to estimate the prognostic impact of pregnancy when breast cancer is diagnosed. We recently described the obstetric and neonatal outcomes of BCP.[24] Here, we used this series to compare survival between women with BCP and patients who did not have associated pregnancies.

PATIENTS AND METHODS

Design, Setting, and Participants

Two international multicenter cohort studies collaborated in this initiative. The German Breast Group (GBG) started a registration study for breast cancer during pregnancy in April 2003. In addition, although separately, the international Cancer in Pregnancy (CIP) study (www.cancerinpregnancy.org) started a registry in 2005 for all types of cancer diagnosed during pregnancy. All registered patients diagnosed with primary BCP between January 1, 2000, and September 30, 2011, were eligible for inclusion, independent of outcome of the pregnancy or treatment of breast cancer. Women with in situ or primary metastatic disease and those relapsing during pregnancy were excluded from all analyses. Women who became pregnant during treatment or received their diagnosis postpartum were also excluded to ensure homogeneity. We compared the patients of both registries to prevent double entries.

Both observational studies were approved by ethics committees, and written informed consent was obtained from patients before prospective inclusion. As regards the retrospective part, a majority of patients were registered without obtaining informed consent. Details on the construct and quality assurance can be found in the Appendix (online only). The studies were registered with ClinicalTrials.gov (CIP study, NCT00330447; GBG study, NCT00196833).

For the nonpregnant comparison group, we recruited all nonpregnant patients with stage I to III disease from the institutional database of the Multidisciplinary Breast Centre, University Hospitals Leuven, Leuven, Belgium, age $\leq$ 45 years, between January 1, 2000, and August 1, 2010 (n = 865).

Clinical Assessment

The patients' disease was staged using the American Joint Committee on Cancer staging system (seventh edition). Diagnosis was made by a combination of ultrasonography, mammography, and/or magnetic resonance imaging, followed by core needle biopsy.[9,24] Type of treatment was decided by the patient's treating physician. To standardize treatment, treatment guidelines were made available by expert opinion reports.[25,26] Both first and senior authors initiated multidisciplinary consensus meetings to construct international guidelines on the treatment of BCP. Whether chemotherapy was administered during pregnancy depended on the gestational age and stage of disease.

Chemotherapy dosages were equal to those for the nonpregnant patients and were based on body surface area. Additional therapies (also administered in the postpartum period), such as trastuzumab, endocrine treatment, and radiation therapy, were collected for all patients. Patient status as of December 31, 2011, was determined by reviewing medical records of patients as well as follow-up requested from the treating physicians, if they were treated elsewhere. We used a predefined case-registration follow-up form, including date of diagnosis, tumor pathologic features, oncologic treatment (including type of surgery and use of chemotherapy, radiotherapy, endocrine therapy, and trastuzumab), and patient outcome (including time and site of metastasis and survival status). For the pregnant patients, gestational age was calculated from the estimated due date, based on first-trimester ultrasound examination when performed, or from the last menstrual period.

Primary outcome was disease-free survival (DFS), defined as time in months from the date of first diagnosis to any invasive locoregional (ipsilateral breast, local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer, any distant recurrence of disease, or any secondary malignancy, whichever occurred first.[27] Patients without events were censored at the date of last contact. Secondary outcome was overall survival (OS), defined as time in months from the date of first diagnosis to death resulting from any cause.[27]

Statistical Analysis

Missing values were imputed once using the method of chained equations to avoid bias and increase efficiency.[28,29] DFS and OS were compared between pregnant and nonpregnant patients using multivariable Cox proportional hazards regression to adjust for age at diagnosis, stage, grading, histologic tumor type, estrogen receptor (ER)/progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, trastuzumab, type of chemotherapy, radiotherapy, and hormone therapy.

Given that the average age at diagnosis was clearly different for pregnant and nonpregnant patients, simply adjusting for age by using age as a covariate may not have been sufficient.[30] Instead, we adjusted for age using inverse probability weighting to statistically correct for the strong imbalance in this variable. We estimated the probability of being pregnant according to age ($P_{pregnant}$) for the patients in the data set. The appropriate transformation of age was determined with the method of fractional polynomials.[31] The weights used in the Cox model were one for pregnant patients and the odds of $P_{pregnant}$ for nonpregnant patients to avoid large and unstable weights.[32,33] This approach succeeded in overcoming the age imbalance, because we observed that the weighted distribution of age was nearly identical for pregnant and nonpregnant patients. A sensitivity analysis in which we adjusted for age using stratification instead of weighting yielded similar results.

Because pregnant patients were recruited in seven countries, we investigated the influence of country by checking the interaction of pregnancy with country (Belgium, Germany, other [including the Netherlands, United Kingdom, Czech Republic, Poland, and Italy]). Exploratory prespecified subgroup analyses were performed by adding interaction terms. Subgroups investigated were ER/PR status, molecular subtype, age, American Joint Committee on Cancer stage, and type of chemotherapy. Finally, one additional analysis compared pregnant patients with nulliparous nonpregnant patients only. All analyses were performed using the SAS statistical software package (version 9.2; SAS Institute, Cary, NC), making use of IVEware (version 0.2; http://www.isr.umich.edu/src/smp/ive/) for imputation of missing values.[34]

RESULTS

There were 447 women with BCP registered, of whom 311 were eligible for this analysis (we excluded three women age $\geq$ 46 years, 36 with primary metastatic disease, 57 diagnosed before 2000, and 40 without follow-up); 240 (77.2%) of 311 patients were included prospectively. These 311 patients were compared with 865 women with breast cancer who were not pregnant (ratio 1:2.78). Demographic features are summarized in Table 1. Distribution of pregnant patients among seven European countries was as follows: Germany, n = 137 (44.05%); Belgium, n = 77 (24.76%); the Netherlands, n = 65 (20.90%); Great Britain, n = 10 (3.22%); Poland, n = 10 (3.22%); Czech Republic, n = 10 (3.22%); and Italy, n = 2 (0.64%). Median age was 33 years (interquartile range, 31 to 36) for the pregnant and 41 years (interquartile range, 38 to 44) for the nonpregnant patients. Median follow-up was 61 months (5 years, 1 month; range, 4 to 135 months).

Table 1. Clinicopathologic Variables

Variable	Pregnant Patients (n = 311)		Nonpregnant Patients (n = 865)		Missing Values			
					Pregnant Patients		Nonpregnant Patients	
	No.	%	No.	%	No.	%	No.	%
AJCC stage					1	0.3	2	0.2
1	48	15.4	263	30.4				
2	177	56.9	399	46.1				
3	86	27.7	203	23.5				
Grade					15	4.8	2	0.2
1	7	2.3	69	8.0				
2	67	21.5	307	35.5				
3	237	76.2	489	5.65				
Histology					4	1.3	1	0.1
IDA		97.4		91.0				
ILA		2.6		9.0				
ER and/or PR positive		46.6		74.5	0	0.0	7	0.8
HER2 positive		31.8		17.0	12	3.9	34	3.9
Triple negative		37.9		19.1	4	1.3	12	1.4

NOTE. Descriptive statistics are reported after imputation of missing values.
Abbreviations: AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDA, invasive ductal carcionoma; ILA, invasive lobular carcinoma; PR, progesterone receptor.

Treatment

Type of treatment is depicted in Table 2. Among the pregnant patients, taxanes were administered to 95 (47.03%) with adjuvant chemotherapy and to 69 (71.13%) with neoadjuvant chemotherapy. Among the nonpregnant patients, taxanes were administered to 168 (30.88%) with adjuvant chemotherapy and to 79 (77.45%) with neoadjuvant chemotherapy. Within the BCP group, 200 patients (64.31%) received chemotherapy during pregnancy, all in the second or third trimester.

Survival

During follow-up, 42 pregnant patients (14%) and 103 nonpregnant patients (12%) died. For the total group (pregnant and nonpregnant patients together), median follow-up for DFS was 61 months. Observed 5-year DFS was 78%, and median DFS time was 131 months. Observed 5-year OS was 87%; median OS time was not reached within the time frame of the study (Fig 1). Table 3 summarizes the effect of pregnancy from the multivariable Cox proportional hazards regression of DFS and OS, adjusted for age at diagnosis, stage, grading, histologic tumor type, ER/PR status, HER2, trastuzumab, and chemotherapy. We did not find evidence of worse prognosis for women diagnosed with BCP regarding disease recurrence (hazard ratio [HR], 1.34; 95% CI, 0.93 to 1.91; $P = .14$) or OS (HR, 1.19; 95% CI, 0.73 to 1.93; $P = .51$). The average 5-year DFS probability based on the multivariable model was 65% for pregnant patients; it would have increased to 71% if these patients had not been pregnant. Likewise, the average 5-year OS probability was 78% for pregnant patients; it would have increased to 81% if these patients had not been pregnant. The sensitivity analysis using stratification rather than weighting for age to account for the strong age differences between pregnant and

Table 2. Breast Cancer Treatment

Treatment	Pregnant Patients (n = 311)		Nonpregnant Patients (n = 865)		Missing Values			
					Pregnant		Nonpregnant	
	No.	%	No.	%	No.	%	No.	%
Surgery					22	7.1	0	0.0
None	2	0.6	10	1.2				
Breast conserving	140	45.0	433	50.1				
Mastectomy	147	47.3	422	48.8				
Chemotherapy setting					8	2.6	0	0.0
None	4	1.3	219	25.3				
Adjuvant	208	66.9	544	62.9				
Neoadjuvant	99	31.8	102	11.8				
During pregnancy	200	64.3	—	—				
Taxanes	169	54.3	247	28.6	1	0.3	0	0.0
Trastuzumab	76	24.8	140	17.0	2	0.6	34	3.9
Radiotherapy	205	73.3	768	88.8	34	10.9	0	0.0
Endocrine therapy	117	41.5	580	67.1	38	12.2	0	0.0

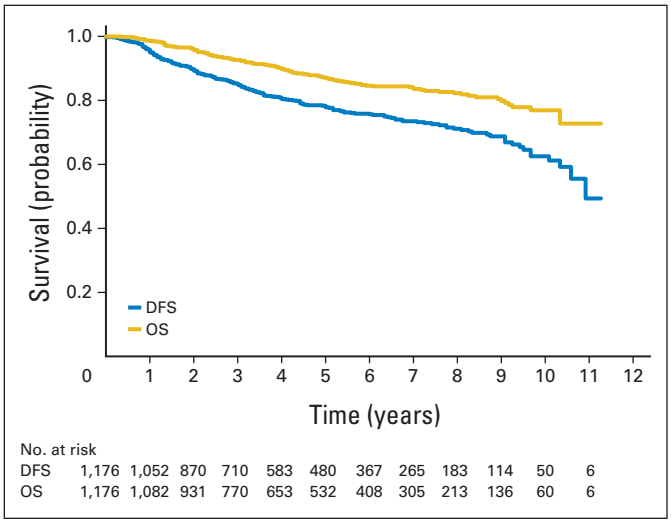

Fig 1. Kaplan-Meier curves for disease-free survival (DFS) and overall survival (OS) for the total group of patients (pregnant and nonpregnant).

nonpregnant patients confirmed these results. There was no clear effect of country of origin of pregnant patients (interaction pregnancy-country $P = .61$ for DFS and .26 for OS; Fig 2). However, the effects were smallest for pregnant patients from Belgium (HR, 1.10 for DFS and 0.98 for OS). The main Cox model resulted in an average predicted 5-year DFS probability of 65% for pregnant patients. According to the model, this would have increased to 71% if these patients had not been pregnant (but all other characteristics were identical). For OS, the average predicted 5-year survival probability would have increased from 78% to 81%.

The subgroup analyses did not suggest clear effects (Fig 2). When comparing pregnant patients with nulliparous nonpregnant patients (n = 200; 23.1%), no differences were found for DFS (HR, 1.58; 95% CI, 0.93 to 2.77) or OS (HR, 1.58; 95% CI, 0.76 to 3.52). The lack of a prognostic effect of pregnancy was present both in the GBG and CIP groups.

DISCUSSION

We documented the prognosis of BCP in the largest series, to our knowledge, collected within the framework of a European collaboration. Tumor characteristics were comparable to other reported results of BCP.[35,36] Poorly differentiated invasive ductal adenocarcinomas were prevalent and often hormone receptor negative. After adjusting for known prognostic factors, we found a modest, if any, effect of pregnancy on DFS and OS. Regarding the DFS analysis, the observed HR of 1.34 suggests better outcome for the nonpregnant group; however, the CI shows that any distinct effect of pregnancy cannot be concluded. Also, the observed HR for OS was only 1.19. This reassuring effect was especially true for the Belgian and German patients (Fig 2). The largest difference was seen in the countries that contributed with lower numbers of patients with BCP. The effect of patient load on the outcome therefore deserves further investigation. The results of this study allow clinicians to inform patients with BCP on their prognosis, if receiving a standard therapy.

Table 3. Cox Proportional Hazards Regression of DFS and OS

Outcome	HR	95% CI	*P*
DFS			
Main analysis: IPW for age	1.34	0.93 to 1.91	.14
Sensitivity analysis: stratification for age	1.31	0.92 to 1.85	.15
OS			
Main analysis: IPW for age	1.19	0.73 to 1.93	.51
Sensitivity analysis: stratification for age	1.06	0.66 to 1.68	.80

NOTE. To account for clustering in data obtained by IPW or stratification, we used robust sandwich variance estimator when fitting Cox proportional hazards model. Age groups used for stratification: ≤ 30, 31 to 35, 36 to 40, and 41 to 45 years.

Abbreviations: DFS, disease-free survival; HR, hazard ratio; IPW, inverse probability weighting; OS, overall survival.

The prognosis of BCP has previously been addressed in several studies. We encountered 11 studies that did not distinguish between breast cancer diagnosed during pregnancy or during the postpartum/lactation period, and these are not discussed further. We reviewed 17 studies published since 1985 that have made a subdifferentiation between breast cancer during and after pregnancy (n = 6)[13,15,16,21-23] or that concentrated solely on BCP, with control groups (n = 7)[11,12,14,17-20] or without control groups (n = 4).[35-38] Probably because of small numbers, the available results are conflicting. Eight of the 17 studies found no difference in survival when compared with the age-matched nonpregnant patients with breast cancer[17-23,36]; six found worse survival for the patients with BCP[11-16]; three observational studies did not comment further on BCP prognosis (Table 4).[35,37,38] Putative factors for worse prognosis included delayed diagnosis and delayed or modified cancer treatment to assure the birth of a healthy infant. Also, the pregnant state with immunosuppression, increased vascularization, and increased hormonal exposure have been postulated as contributing factors. During pregnancy, significantly increased concentrations of estrogen, progesterone, and insulin-like growth factor 1 are present. These hormones are highly linked to breast cancer development and progression.[39] However, on the basis of our results, these factors do not seem to contribute significantly to tumorigenesis or accelerated growth in vivo, as previously thought. Our findings are in agreement with those of Schedin[40] and Lyons et al,[41] who hypothesized that mammary gland involution, rather than pregnancy per se, was crucial for breast cancer growth. The postpartum or postlactation breast involution relies on tissue-remodeling processes of wound healing and inflammation that also have a pro-oncogenic effect and promote tumor-cell dissemination. Thus, postpartum breast cancer rather than BCP carries a worse prognosis. How long this increased risk persists in the postpartum period has not been identified; the effect has been reported as continuing up to 10 years before a cross-over effect occurs, and the previous pregnancy becomes a protective factor.[16,42] Also, for first-time mothers age > 35 years, the risk is permanently increased when compared with nulliparous women. The fact that the majority of our nonpregnant patients were parous (76.9%) might be regarded as a confounding factor, because we did not take time since last pregnancy into account. However, as suggested by Borges and Schedin,[43] we also compared pregnant patients with nulliparous nonpregnant patients (23.1%), and no differences in DFS or OS were found.

Gestational physiologic changes alter the pharmacokinetics of chemotherapy during pregnancy. In a pilot study, we calculated that

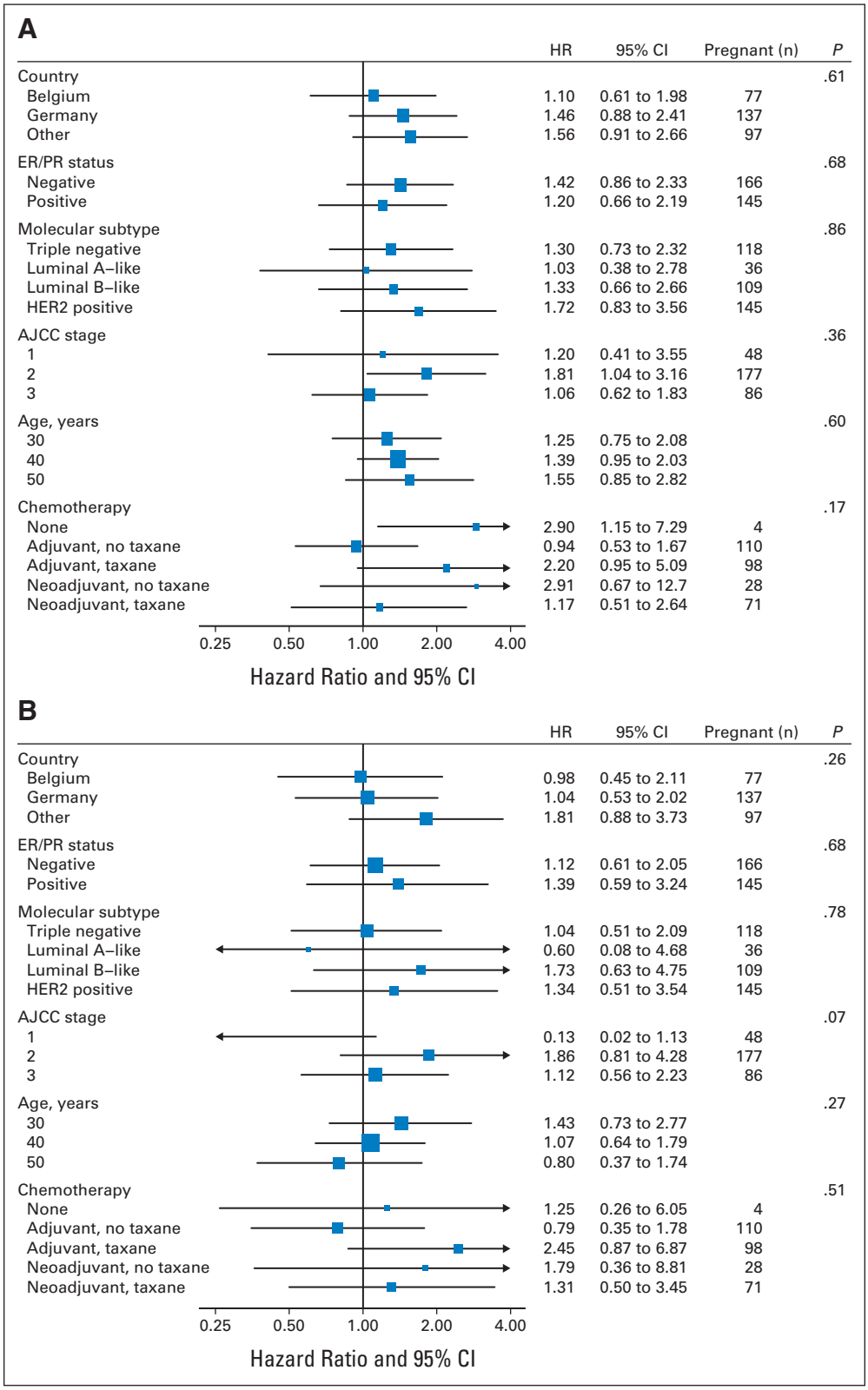

Fig 2. Forest plots with results of the effect of country of origin of pregnant patients and of prespecified subgroup analyses for (A) disease-free and (B) overall survival. AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PR, progesterone receptor.

Table 4. Outcome Rates of Breast Cancer During Pregnancy As Reported in Literature Since 1985*

Study	Year	Total Patients: Pregnant No.	Pregnant %	Postpartum No.	Postpartum %	Nonpregnant No.	Follow-Up Period	DFS (%): Pregnant	DFS (%): Nonpregnant	OS (%): Pregnant	OS (%): Nonpregnant	Authors' Conclusion
Nugent and O'Connell[17]	1985	19				155	5 years			57	56	No difference in OS
Greene[18]	1988	8				36	90 months			87.5	91.7	No difference in OS
Tretli et al[13]	1988	20	57	15	43	40	4 years			15	60	Worse survival for BCP
Guinee et al[12]	1994	26				139	5 years			40	74	Worse survival for BCP
Ezzat et al[19]	1996	28				84	7 years	37	33	57	61	No difference in DFS or OS
Ibrahim et al[20]	2000	72				216	47.5 months			67	58	No difference in DFS or OS
Bladström et al[11]	2003	94				7,779	10 years			43.9	68.6	Worse DFS and OS for BCP
Middleton et al[35]	2003	39					43 months	56		80		—
Ring et al[38]	2005	28					40.5 months	63		67		—
Hahn et al[37]	2006	57					38.5 months	70.2		77		—
Mathelin et al[15]	2008	18	45	22	55	61	10 years			72	97	Worse DFS and OS for BCP
Stensheim et al[22]	2008	59	56	46	44	13.106	4.9 years			56	69	No difference in OS
Beadle et al[21]	2009	51	49	53	51	668	91 months			62.6	64.6	No difference in OS
Halaska et al[23]	2009	16	50	16	50	32	142 months	81.3	62.5	87.5	71.9	No difference in DFS or OS
Cardonick et al[36]	2010	130					3.14 years			Stage I, 100; stage II, 86; stage III, 86; stage IV, 0		Survival for stages I to III seems similar to nonpregnant survival rates according to American Cancer Society Surveillance Research
Johansson et al[16]	2011	107	10	1,003	90	14.611						Worse survival for BCP
Azim et al[14]	2012	65				130	5 years	52.1	74.3	79.6	88.4	Significantly poorer DFS for BCP; no difference in OS observed
Current study		311				865	5 years	65	71	78	81	No difference in DFS or OS

NOTE. Table shows 17 studies with survival outcome of patients with BCP published since 1985; for studies making subdifferentiation between breast cancer during and after pregnancy (percentages specified), results of DFS and OS for postpartum and lactating patients with breast cancer are not shown, because this was not the aim of our study.[13,15,16,21-23]

Abbreviations: BCP, breast cancer during pregnancy; DFS, disease-free survival; OS, overall survival.

*Postpartum breast cancer excluded.

for four cytotoxic drugs, including anthracyclines and taxanes, maximum concentration and the area under the curve were lower in pregnant women.[44] Although these alterations may theoretically influence maternal prognosis, we decided in an international consensus meeting focused on BCP that until more data are available, chemotherapy dosages for pregnant women should be calculated based on actual height and weight.[26] A previous analysis of our cohort showed that among the patients with BCP, survival rates did not differ between those who received chemotherapy during pregnancy and those who did so during the postpartum period.[24] The similar outcomes calculated in this series between pregnant (64% of patients received chemotherapy during pregnancy; n = 200) and nonpregnant women is similarly reassuring. These observations suggest that chemotherapy during pregnancy can be administered as it is in nonpregnant women (with chemotherapy dosing based on body surface area), despite the altered pharmacokinetics during pregnancy.[26]

Apart from maternal safety, fetal safety is also considered when patients are counseled. Chemotherapy exposure during the second and third trimesters of pregnancy did not impair neonatal outcome. The rate of congenital malformations was not increased, although the neonates were more commonly born before the 37th week of gestation (49.6% compared with 10% to 15% in the general population).[24] Long-term cardiac and neurodevelopmental assessments of children exposed to chemotherapy in utero prospectively have been documented. A recent interim analysis did not show sequelae, although prematurity was associated with impaired cognitive development.[10] Taken together, the available data confirm maternal and fetal safety when breast cancer is treated during pregnancy. Standard treatment during pregnancy, including chemotherapy, adds to an optimal maternal outcome. This outcome now seems to be comparable to that of nonpregnant patients. In addition, the administration of chemotherapy during pregnancy contributes to fewer preterm deliveries and thus also to improved fetal outcome.

Our study design has some limitations. Data were retrospectively pooled from different hospitals from different countries. The control group came from one hospital only. However, it was chosen to create a more homogeneous control group, with few missing data. Histologic data were not centrally confirmed, and information on family history of breast cancer was sparse. However, our study design precludes the small-sample bias and heterogeneity of previous studies, which have been the major limitations to drawing firm conclusions.

In conclusion, in the largest cohort study to date, to our knowledge, we found similar survival for patients with primary breast cancer diagnosed during pregnancy, when compared with nonpregnant patients with breast cancer, after adjusting for known prognostic factors. The observation that patients with BCP experience survival rates comparable to those of nonpregnant patients is important when they are counseled. Breast cancer treatment during pregnancy does not jeopardize maternal prognosis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked

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REFERENCES

1. Smith LH, Danielsen B, Allen ME, Cress R: Cancer associated with obstetric delivery: Results of linkage with the California cancer registry. Am J Obstet Gynecol 189:1128-1135, 2003
2. Van Calsteren K, Heyns L, De Smet F, et al: Cancer during pregnancy: An analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. J Clin Oncol 28:683-689, 2010
3. Wallack MK, Wolf JA Jr, Bedwinek J, et al: Gestational carcinoma of the female breast. Curr Probl Cancer 7:1-58, 1983
4. Lethaby AE, O'Neill MA, Mason BH, et al: Overall survival from breast cancer in women pregnant or lactating at or after diagnosis: Auckland Breast Cancer Study Group. Int J Cancer 67:751-755, 1996
5. Cheesman WS: Influence of pregnancy on cancer of the breast. Ann Surg 46:487-488, 1907
6. Haagensen CD, Stout AP: Carcinoma of the breast: II. Criteria of operability. Ann Surg 118:859-870, 1943
7. White TT: Carcinoma of the breast and pregnancy: Analysis of 920 cases collected from the literature and 22 new cases. Ann Surg 139:9-18, 1954
8. Cardonick E, Iacobucci A: Use of chemotherapy during human pregnancy. Lancet Oncol 5:283-291, 2004
9. Amant F, Loibl S, Neven P, et al: Breast cancer in pregnancy. Lancet 379:570-579, 2012
10. Amant F, Van Calsteren K, Halaska MJ, et al: Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: An observational study. Lancet Oncol 13:256-264, 2012
11. Bladström A, Anderson H, Olsson H: Worse survival in breast cancer among women with recent childbirth: Results from a Swedish population-based register study. Clin Breast Cancer 4:280-285, 2003
12. Guinee VF, Olsson H, Möller T, et al: Effect of pregnancy on prognosis for young women with breast cancer. Lancet 343:1587-1589, 1994
13. Tretli S, Kvalheim G, Thoresen S, et al: Survival of breast cancer patients diagnosed during pregnancy or lactation. Br J Cancer 58:382-384, 1988
14. 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 51:653-661, 2012
15. Mathelin C, Annane K, Treisser A, et al: Pregnancy and post-partum breast cancer: A prospective study. Anticancer Res 28:2447-2452, 2008
16. 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 20:1865-1872, 2011
17. Nugent P, O'Connell TX: Breast cancer and pregnancy. Arch Surg 120:1221-1224, 1985
18. Greene FL: Gestational breast cancer: A ten-year experience. South Med J 81:1509-1511, 1988
19. Ezzat A, Raja MA, Berry J, et al: Impact of pregnancy on non-metastatic breast cancer: A case control study. Clin Oncol (R Coll Radiol) 8:367-370, 1996
20. Ibrahim EM, Ezzat AA, Baloush A, et al: Pregnancy-associated breast cancer: A case-control study in a young population with a high-fertility rate. Med Oncol 17:293-300, 2000
21. Beadle BM, Woodward WA, Middleton LP, et al: The impact of pregnancy on breast cancer outcomes in women ≤ 35 years. Cancer 115:1174-1184, 2009
22. 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 27:45-51, 2009
23. Halaska MJ, Pentheroudakis G, Strnad P, et al: Presentation, management and outcome of 32 patients with pregnancy-associated breast cancer: A matched controlled study. Breast J 15:461-467, 2009
24. Loibl S, Han SN, von Minckwitz G, et al: Treatment of breast cancer during pregnancy: An observational study. Lancet Oncol 13:887-896, 2012
25. Loibl S, von Minckwitz G, Gwyn K, et al: Breast carcinoma during pregnancy: International recommendations from an expert meeting. Cancer 106:237-246, 2006
26. Amant F, Deckers S, Van Calsteren K, et al: Breast cancer in pregnancy: Recommendations of an international consensus meeting. Eur J Cancer 46:3158-3168, 2010
27. Hudis CA, Barlow WE, Costantino JP, et al: Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: The STEEP system. J Clin Oncol 25:2127-2132, 2007
28. White IR, Royston P, Wood AM: Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 30:377-399, 2011
29. Sterne JA, White IR, Carlin JB, et al: Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. BMJ 338:b2393, 2009
30. Rubin DB: Using propensity scores to help design observational studies: Application to the tobacco litigation. Health Serv Outcomes Res Methodol 2:169-188, 2001
31. Sauerbrei W, Royston P, Binder H: Selection of important variables and determination of functional form for continuous predictors in multivariable model building. Stat Med 26:5512-5528, 2007
32. Austin PC: An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 46:399-424, 2011
33. Morgan SL, Todd JL: A diagnostic routine for the detection of consequential heterogeneity of causal effects. Sociol Methodol 38:231-281, 2008
34. van Buuren S: Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 16:219-242, 2007
35. Middleton LP, Amin M, Gwyn K, et al: Breast carcinoma in pregnant women: Assessment of clinicopathologic and immunohistochemical features. Cancer 98:1055-1060, 2003
36. Cardonick E, Dougherty R, Grana G, et al: Breast cancer during pregnancy: Maternal and fetal outcomes. Cancer J 16:76-82, 2010
37. Hahn KM, Johnson PH, Gordon N, et al: Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer 107:1219-1226, 2006
38. Ring AE, Smith IE, Jones A, et al: Chemotherapy for breast cancer during pregnancy: An 18-year experience from five London teaching hospitals. J Clin Oncol 23:4192-4197, 2005
39. Rossouw JE, Anderson GL, Prentice RL, et al: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA 288:321-333, 2002
40. Schedin P: Pregnancy-associated breast cancer and metastasis. Nat Rev Cancer 6:281-291, 2006
41. Lyons TR, Schedin PJ, Borges VF: Pregnancy and breast cancer: When they collide. J Mammary Gland Biol Neoplasia 14:87-98, 2009
42. Janerich DT, Hoff MB: Evidence for a cross-over in breast cancer risk factors. Am J Epidemiol 116:737-742, 1982
43. Borges VF, Schedin PJ: Pregnancy-associated breast cancer: An entity needing refinement of the definition. Cancer 118:3226-3228, 2012
44. Van Calsteren K, Verbesselt R, Ottevanger N, et al: Pharmacokinetics of chemotherapeutic agents in pregnancy: A preclinical and clinical study. Acta Obstet Gynecol Scand 89:1338-1345, 2010

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