Effect of Pregnancy on Overall Survival After the Diagnosis of Early-Stage Breast Cancer

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Purpose: To evaluate the impact of subsequent pregnancy on the prognosis of patients with early breast cancer.

Patients and Methods: One hundred eight patients who became pregnant after diagnosis of early-stage breast cancer were identified in institutions participating in International Breast Cancer Study Group (IBCSG) studies. Fourteen had relapse of breast cancer before their first subsequent pregnancy. The remaining 94 patients (including eight who relapsed during pregnancy) formed the study group reported here. A comparison group of 188 was obtained by randomly selecting two patients, matched for nodal status, tumor size, age, and year of diagnosis from the IBCSG database, who were free of relapse for at least as long as the time between breast cancer diagnosis and completion of pregnancy for each pregnant patient. Survival comparison used Cox proportional hazards regression models.

Results: Overall 5- and 10-year survival percentages (± SE) measured from the diagnosis of early-stage breast cancer among the 94 study group patients were 92% ± 3% and 86% ± 4%, respectively. For the matched comparison group survival was 85% ± 3% at 5 years and 74% ± 4% at 10 years (risk ratio, 0.44; 95% confidence interval, 0.21 to 0.96; P = .04).

Conclusion: Subsequent pregnancy does not adversely affect the prognosis of early-stage breast cancer. The superior survival seen in this and other controlled series may merely reflect a healthy patient selection bias, but is also consistent with an antitumor effect of the pregnancy.


Breast cancer is responsive to various endocrine changes. About one quarter of cases occur before the menopause. Pregnancy provides a complex series of endocrine changes affecting levels of estrogen and progesterone and the gonadotrophin axis, and also involves alterations in growth factors and immunologic competence. Patients who wish to bear children after treatment for primary breast cancer may seek advice as to whether pregnancy increases their chances of disease recurrence. Previously available data and reviews are, in general, reassuring that no increased risk of death from breast cancer has been demonstrated in women who are pregnant when diagnosed or later become pregnant.1-17 However, the number of patients studied remains small, and most studies lack a comparison group of patients who did not become pregnant, making it difficult to interpret the outcome data. There is a particular paucity of data involving explicit comparison with a relevant nonpregnant group.7,8,12,13

We wished to ascertain the effect of subsequent pregnancy in women with early-stage breast cancer. Ultimately, such information should assist women and their clinicians in reaching decisions about pregnancy after breast cancer. We therefore conducted a retrospective review of survival for women who became pregnant after treatment for early-stage breast cancer in institutions associated with the International Breast Cancer Study Group (IBCSG), in comparison with that of matched patients selected from among IBCSG trial participants.

Patients and Methods

Study Design

International Breast Cancer Study Group investigators were asked to retrospectively identify patients from their practices who had become pregnant after the diagnosis of invasive breast cancer, whether these

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patients had been included in IBCSG studies or not. The clinicians completed a form for each patient recording information regarding patient characteristics before diagnosis (age at menarche, prior pregnancies, family history of breast cancer), information on subsequent pregnancies, characteristics of disease at diagnosis, initial breast cancer treatment, recurrences, current disease and survival status. One hundred eight pregnant patients were identified, of whom 24 had been enrolled in IBCSG studies. Fourteen of the 108 women had recurrence of their breast cancer (eight local, two regional, two contralateral breast, and two distant) before the completion of their first subsequent pregnancy. These 14 patients were excluded from the main comparison. For each of the remaining 94 patients (the study group), we selected from IBCSG trials two matched patients who did not have a subsequent pregnancy (the comparison group). The IBCSG studies evaluated similar prognostic groups and were open at the time of the diagnosis of the corresponding pregnant patient in the study group.

The patients in the comparison group were selected from the randomized IBCSG Trials V, 18, 19 VI, 20 and VIII 21 that were initiated in 1981, 1986, and 1990, respectively, to evaluate systemic adjuvant therapies (chemotherapy and endocrine therapy) for premenopausal women with operable breast cancer. Trial V randomized both node-positive and node-negative patients. The 715 node-positive patients received one of three adjuvant treatments: a single cycle of perioperative chemotherapy with IV CMF (cyclophosphamide 400 mg/m² IV days 1 and 8; methotrexate 40 mg/m² IV days 1 and 8; 5-fluorouracil 600 mg/m² IV days 1 and 8), plus leucovorin (15 mg IV 24 hours after day 1 and 15 mg PO 24 hours after day 8); six cycles of conventional timed classic CMF (cyclophosphamide 100 mg/m² orally days 1 and 14; methotrexate 40 mg/m² IV days 1 and 8; 5-fluorouracil 600 mg/m² IV days 1 and 8) plus prednisone (7.5 mg orally daily) repeated every 28 days for six cycles; or both one cycle of perioperative chemotherapy plus six cycles of conventionally timed classic CMF plus prednisone.18 The 692 node-negative patients in Trial V received either the one cycle of perioperative chemotherapy or no adjuvant chemotherap[y.19 The IBCSG Trial VI had a factorial design testing three versus six cycles of classical CMF and reintroduction versus no reintroduction of three additional cycles of CMF at 3-month intervals; 1,475 node-negative, premenopausal patients were accrued to this study.20 In Trial VIII 1,111 node-negative premenopausal patients were randomly assigned to receive one of three GnrH analogs: a GnrH analog for 2 years, or six cycles of classical CMF, or six cycles of classical CMF followed by 18 months of a GnRH analog.21

The hierarchy used to make the randomly assigned matches was as follows:

1. Disease-free interval (disease-free interval for comparison group patients equal to or longer than the time from diagnosis to pregnancy completion);
2. Nodal status: 0, 1-3, 4-6, or greater than 7 involved nodes;
3. Tumor size: less than 1, 1 to less than 3, 3 to less than 5, greater than or equal to 5 cm maximal tumor diameter;
4. Age at diagnosis in decades;
5. Year of diagnosis.

The matched comparison group for the 94 study patients had a disease-free interval at least equal to the time between diagnosis of breast cancer and delivery (or abortion) of the corresponding pregnant patient. If an exact match was not possible, we attempted to select a comparison patient with a more favorable prognosis (fewer positive nodes, smaller tumor size, older age at diagnosis). The most frequent reason for inability to find an exact match was age, because patients who became pregnant were diagnosed at a younger age than most patients in the IBCSG database. Thus, when a comparison patient diagnosed in her twenties was not available, one diagnosed in her thirties was used. For three cases we were unable to select a comparison patient with a more favorable prognosis in the category of tumor size and chose a comparison patient with a tumor size from the next larger category. Year of diagnosis was matched within 2 years except for five patients diagnosed before 1979 who were matched within 4 to 8 years.

Statistical Methods

Survival curves measured from the date of breast cancer diagnosis were prepared using the Kaplan-Meier method.22 Differences in survival between the study group and the comparison group were evaluated using a Cox proportional hazards regression model23 controlling for tumor size, nodal status, and age at diagnosis. Inasmuch as each pregnant patient and her matched comparisons have an immortal person time equal to the time from diagnosis to pregnancy, this was subtracted from the overall survival time for each member of the triplet before fitting the model. Overall survival was calculated as the time from breast cancer diagnosis until death from any cause, or date of last survival update. All P values were two-sided.

RESULTS

Patient Characteristics

The 94 patients in the study group had a total of 137 pregnancies after breast cancer diagnosis. Sixty-seven patients had one pregnancy; 17 patients had two; seven patients had three; two patients had four; and one patient had seven pregnancies after breast cancer diagnosis. There were 89 pregnancies resulting in live births (88 singletons and one set of triplets), one stillbirth, 33 therapeutic abortions (23 recorded as recommended by the doctor), 12 spontaneous abortions, and two pregnancies ongoing at the time of data submission. Seventy-three of the women had at least one full-term pregnancy, but for three of these women the exact date of delivery was unknown. Twenty-seven of the 94 women were known to have nursed, 25 had not, and 42 had unknown nursing status. Of the 85 cases with recorded family histories, 11 (12.9%) reported a breast cancer in a first-degree relative.

Study Group Breast Cancer Characteristics and Treatment

The mean interval (± SD) from diagnosis of breast cancer to completion of first subsequent pregnancy was 33.0 ± 21.1 months (median, 27.8 months). Forty-three percent of the women completed their pregnancy (birth or abortion) within 2 years of their diagnosis (Table 1). Details of disease extent and treatment were incomplete in this retrospectively identified cohort. Information was missing on tumor size (nine patients), number of involved lymph nodes (four patients), estrogen receptor (ER) status (32 patients), progesterone receptor (PgR) status (44 patients), type of surgery (one patient), age at menarche (20 patients), and family history of cancer (nine patients). From the known
cases, the mean tumor size was 2.7 ± 1.5 cm), and the mean number of involved lymph nodes was 1.9 ± 4.1. Estrogen receptor status was positive in 40 patients (65% of those with a known value), and PgR status was positive in 27 (54%) patients. Many women were diagnosed before the routine assessment of ER and PgR. Mastectomy was the definitive surgery in 63 (68%) patients. Adjuvant radiation therapy was reported for 26 patients, and adjuvant chemotherapy, for 55 patients. The chemotherapy used was a combination of cyclophosphamide, methotrexate, and fluorouracil (CMF) in 52 patients. Only three patients were reported to have received adjuvant endocrine therapy, which was not routinely administered to premenopausal women during most of the study period.

Eight of the 94 pregnant patients experienced a recurrence of their breast cancer during pregnancy, four of them in the 2 months before delivery (or abortion). Twenty-seven other patients in the study group had breast cancer recurrence after completion of a pregnancy.

**Study Group Overall Survival**

At a median follow-up of 7.4 years from initial breast cancer diagnosis, 11 patients in the study group had died (four of 50 with node-negative disease; seven of 40 with node-positive disease). All but one of the deaths was considered disease related. Five of the 11 deaths occurred among the eight women whose breast cancer recurred during the first pregnancy after diagnosis of breast cancer. No deaths were observed among the nine patients who had an interval exceeding 5 years between breast cancer diagnosis and subsequent pregnancy. The 5-year survival (±SE) calculated from initial diagnosis of breast cancer was 92% ± 3%, and the 10-year survival was 86% ± 4% (Fig 1).

**Comparison With the Matched Comparison Group**

The characteristics of the 94 study group patients and of the 188 patients selected from the IBCSG database to form the matched comparison group are given in Table 2. Survival of the women who became pregnant was superior to the matched group, for which the 5-year survival (±SE) was 85% ± 3% and the 10-year survival was 74% ± 4%.
The Cox proportional hazards regression model, controlling for nodal status, tumor size, and age at diagnosis, yielded a risk ratio of 0.44 (95% confidence interval [CI], 0.21 to 0.96; \( P = .04 \)). Overall survival for the study group was not compromised compared with the comparison group for either the 73 women who had at least one full-term pregnancy (10-year survival 85% ± 5% versus 79% ± 4%) or for the 21 women who had less than a full-term pregnancy (10-year survival 91% ± 9% versus 51% ± 10%).

### DISCUSSION

This study reinforces previous reports that there appears at least to be no adverse effect of subsequent pregnancy on the prognosis of women with breast cancer. Indeed there is suggestive evidence that pregnancy may be associated with a more favorable outcome. Using matched comparisons, the present study showed a lower risk of death for the pregnant group, with a risk ratio for death of 0.44 (95% CI, 0.21 to 0.96; \( P = .04 \)).

Two Scandinavian studies using population-based controls yielded remarkably similar results. The Swedish study showed a relative risk of death for patients who became pregnant compared with controls of 0.48 (95% CI, 0.18 to 1.29),\(^7\) whereas the Danish study found a relative risk of 0.55 (95% CI, 0.28 to 1.06).\(^13\) A Finnish population-based matched survival study of women who delivered a liveborn child subsequent to the cancer diagnosis reported a larger decrease in the risk of death with a relative risk of 0.21 (95% CI, 0.10 to 0.45).\(^15\) The investigators interpreted the result as a “healthy mother” effect. A recently published population-based study conducted in the United States evaluated survival of 53 women who became pregnant after breast cancer compared with matched controls. The results again suggest that pregnancy after a diagnosis of breast cancer does not have an adverse effect on survival, with a relative risk of 0.80 (95% CI, 0.3 to 2.3).\(^16\)

Ezzat et al\(^8\) reported results from another study that included comparison with a control group and also found a nonsignificant trend in favor of the pregnant patients. Their study was limited to patients whose breast cancer was diagnosed during pregnancy. It might be expected that reduction in risk of death associated with any protective effect of pregnancy would be less marked in these patients, because the tumor had by definition been diagnosed despite pregnancy, and in most cases would have progressed during pregnancy. Despite this, a slight favorable trend for patients diagnosed during pregnancy was found.

Formal meta-analysis of these five controlled studies would be difficult to interpret because of their differing designs and inclusion criteria. Nevertheless, a trend to a survival benefit with subsequent pregnancy was seen in all the controlled studies. It may merely represent a “healthy patient” bias, in that women with less subclinical tumor load, and therefore a superior prognosis, may be more likely to attempt or to achieve subsequent pregnancy.
tively, there may be a real biologic beneficial effect that is unexplained.

There are several limitations to our study. Because no defined group exists from which patients could be selected, the pregnant study group patients came from both inside and outside the IBCSG trials, whereas all comparison group patients were enrolled in these trials. Thus, the possibility of selection bias cannot be excluded. The use of a matched comparison group, however, may reduce the impact of such bias. In each instance, the comparison group patients were selected such that they had more favorable prognostic features than the corresponding pregnant patient. Nevertheless, case ascertainment bias cannot be ruled out. For example, institution was not used in the matching process, and different survival according to institution might influence the results. A higher percent of women in the comparison group received chemotherapy and a lower percent reported a family history of breast cancer compared with the study group. The difference in chemotherapy use reflects the fact that the comparison group patients were selected exclusively from the IBCSG trials, which were designed to evaluate chemotherapy. Thus, the increased use of chemotherapy does not reflect selection of patients with a worse prognosis. In fact, it is unlikely that women in the comparison group were at greater risk for recurrence as our matching algorithm biased the comparison group patient to have a better prognosis based on known risk factors. The lower rate of family history reported for the comparison group might also tend to bias the results in favor of this group. In addition, matching on age and tumor size was not complete, and other factors that could influence outcome could also be unbalanced between study and comparison groups.

Whatever they may decide about the personal and social aspects of having a child while facing an uncertain future, women with breast cancer who wish to undertake further pregnancies should be reassured that the available evidence shows pregnancy will not adversely affect their survival.

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