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Pregnancy After Breast Cancer

Mary L. Gemignani, MD, and Jeanne A. Petrek, MD

The diagnosis and treatment of breast cancer present unique considerations for women who are considering childbearing.

Background: The issue of pregnancy following the diagnosis and treatment of breast cancer is important because the incidence of breast cancer is increasing in women of childbearing age. The fact that many women are delaying childbearing, whether for educational, professional, or personal reasons, increases the number of women who will undergo breast cancer treatment before completing childbearing.

Methods: Data on pregnancy in breast cancer survivors are limited and consist only of retrospective data. This paper reviews the published literature on the influence of subsequent pregnancy on breast cancer, including three recent large-scale population-based studies.

Results: The survival of women with breast carcinoma who subsequently become pregnant is not reported to be decreased in any of the published series. However, several biases may be present that justify the concern regarding the conclusions.

Conclusions: Further research on the safety of subsequent pregnancy after breast carcinoma treatment is needed. To address these issues, patients are currently being accrued for a large, prospective, multicenter study of young breast carcinoma patients.

Introduction

The issue of safety following the treatment of breast cancer is of concern for the breast cancer survivor as well as for the physician involved in her care. Because many women are delaying childbearing for different reasons (educational, professional, and personal), it is becoming increasingly more common for them to undergo breast cancer diagnosis and treatment before initiating or completing childbearing. The delay in childbearing to 30 to 40 years of age is concordant with an increasing incidence of breast cancer in those ages. Of the 178,700 new cases of breast cancer estimated for 1998, 10% to 20% will occur in women of childbearing age.¹ Physicians have stressed the complete rehabilitation of breast carcinoma patients, including reconstruction and psychosocial aspects. It is thus natural following the completion of therapy for the patient to inquire about pregnancy and childbearing.

The hormonal influence on mammary carcinogenesis is well known. The effects of first full-term pregnancy, age at menarche/menopause, and the use of postmenopausal hormone replacements are significant hormonal factors in the pathogenesis of breast cancer. In fact, the importance of the endogenous hormonal milieu on breast cancer promotion has been recognized for more than 100 years. In 1896, Beatson² noted the regression with oophorectomy in premenopausal patients with advanced local disease. The effects of estrogen on causing acceleration of the growth rate of micrometastases, stimulation of dormant micrometastases, or direct carcinogenesis of a new primary are of concern in patients with breast cancer. Few studies have addressed the effects of endogenous hormones in women who become pregnant after breast cancer treatment. Several retrospective studies have included only a limited number of patients, and population-based studies have only recently been published. A large, prospective, multicenter study that is currently ongoing will help to address some of these issues.

Retrospective Series

The earlier literature stated that at least 7% of women who did not undergo oophorectomy underwent one or more pregnancies, and 70% of these pregnancies were to be expected in the first five years after cancer treatment.³ Adjuvant cytotoxic chemotherapy depletes the number of fertile patients, but as many as 11% had a deliberate or unplanned pregnancy in a short-term chemotherapy study.⁴ From the limited available literature, it has been generally observed that breast cancer patients who subsequently become pregnant have good survival rates, often the same or sometimes better than patients with no subsequent pregnancy.^{5,6}

The limited data on outcome after subsequent pregnancy in breast carcinoma patients are derived from retrospective studies, some of which employ case-matching methodology in an attempt to eliminate the obvious bias of pregnancy occurring in those with the better prognosis.

Single institutions have conducted sporadic retrospective studies, each composed of fewer than 100 patients. In 1954, White⁷ reported that eight (67%) of the patients who became pregnant lived at least five years and 58% survived 10 years. In 1962, a series of 52 patients from Memorial Hospital had an overall five-year survival rate of 52%.⁸ Another similar-sized study reported in 1969⁹ included 53 patients with five- and 10-year survival rates of 77% and 69%, respectively. In 1970, Cooper and Butterfield¹⁰ reported a 75% five-year survival rate in 32 patients, and 50% of patients in a 1973 series survived five years.¹¹

Case-matching studies were also performed to lessen the influence of pregnancy occurring only in those with a good prognosis. In 1965, Peters and Meakin¹² matched 96 patients with subsequent pregnancy over several decades with patients with similar age and clinical stage. The patients with subsequent pregnancy had a longer disease-free and overall survival than those without subsequent pregnancy. In the 1970 Cooper and Butterfield analysis,¹⁰ each of 40 patients who subsequently became pregnant were matched with two control subjects as determined by the clinical stage, age, status of lymph node involvement, and equal survival at least to the time of pregnancy. The patients with subsequent pregnancy had a survival time superior to that of the control subjects.

Memorial Sloan-Kettering Cancer Center reported an 80% five-year survival rate for stage I and II (AJCC classification) patients after subsequent pregnancy. The study included 41 patients collected over 30 years. No detrimental effect of subsequent pregnancy was noted, even among patients with positive axillary lymph nodes or among those whose pregnancy occurred less than two years following mastectomy.¹³ In a 1986 nationwide French study,¹⁴ the 10-year survival rate of 68 patients who had subsequent pregnancies was 71%. The survival of the negative-node patients was 90% at 10 years with no difference between cases and controls.

In 1989, Ariel and Kempner¹⁵ found that subsequent pregnancies did not affect overall prognosis in a large private practice experience. The largest series¹⁶ included 136

patients diagnosed over five decades at the Princess Margaret Hospital in Toronto and is an update of the series reported by Peters and Meakin in 1965.¹² They reported an excellent overall 5-year survival rate of 78%.

Data on subsequent pregnancy have also been reported in the analysis of adjuvant chemotherapy trials. Recurrence rates and survival for patients who underwent subsequent pregnancy were similar to those who did not.⁴ A recent study from Athens was reported with 21 patients under the age of 35 years who had a pregnancy after treatment for breast cancer. The recurrence rate and survival of the 21 women was similar to patients of similar age and stage without pregnancy.¹⁷

Three groups of investigators in the recent reports have examined the question of the timing of the subsequent pregnancy on breast cancer prognosis. The effect of interval length between breast cancer diagnosis and pregnancy affects prognosis because women who defer a pregnancy for many years are also those who have remained disease-free for greater period of time.

Clark and Chua¹⁶ found that 72% of their patients became pregnant within two years of treatment. Those who became pregnant within six months had a comparatively poor prognosis — a 54% five-year survival rate compared to a 78% five-year survival rate among those who waited six months to two years to become pregnant after breast cancer diagnosis. Those who waited five years or more to become pregnant had 100% five-year survival from that point. They concluded that a wait of at least six months from completion of treatment is recommended. The data are consistent with the fact that the longer survival after diagnosis is, per se, an indicator of the patients' better prognosis (whether pregnancy occurs or not). The recent French series¹⁴ and the Memorial Hospital series,¹³ which are smaller in number, do not find a statistically significant difference between outcome of patients based on the interval.

How much reliance can be placed on these reports to allow us to adequately advise patients on subsequent pregnancy after breast cancer treatment? Since pregnancy is not coded as a disease or coded in any other way by the record room or tumor registry, cases over the previous decades are all found by memory, as is the situation with the Memorial Hospital series.¹³ Even if a chart or tumor registry review of all premenopausal women had been undertaken, the occurrence of subsequent pregnancy may not be noted.

The Methods section of all of the retrospective series ignores the question of the denominator, the total number of patients with subsequent pregnancies. The most recent and largest series states simply, "We have reviewed patients whose case histories are currently available."¹⁶ Since cases over the decades have been obtained in these reports from the many clinicians' memories, and since it is human nature to remember those who have been seen more recently, the design of these studies is predisposed to find and report on the patients who are alive, which is a recollection bias.

For all of these reasons, each report contains a small fraction of such patients from that institution. An example is a typical series from the Memorial Sloan-Kettering Cancer Center: over 30 years, 41 stage I and II patients were found who became pregnant after breast cancer treatment, and they had an outstanding 80% five-year survival.¹³ However, based on the numbers and ages of women seen in those 30 years, as we were able to obtain from the Memorial Hospital Tumor Registry, and assuming only 7% of breast cancer patients less than 40 years of age became pregnant, this study should have reported on at least 450 women. Therefore, the patients reported from Memorial Hospital represent a highly selected subset, possibly 10% or so of the total who became pregnant after breast cancer treatment.

Population-Based Reports

In an effort to avoid recollection bias, three large, population-based studies¹⁸⁻²⁰ have been published in the last five years. These studies are similar because they all depend on the National Health Service record keeping and a unique identifying number that is assigned to each person at birth and is used for every hospitalization and reportable event such as a cancer diagnosis.

The Finnish population-based study¹⁸ used the personal identification numbers of women with a breast cancer diagnosis and searched the national birth certificate database for the years following their diagnosis. They found 91 eligible patients with subsequent deliveries and matched 471 control subjects for stage, age, and year of breast cancer diagnosis. The control subjects had to be alive for the same time interval as that from diagnosis to delivery of their matched cases. Breast cancer survivors with a subsequent birth after their diagnosis had statistically better survival rates than control subjects of the same age and stage with no subsequent births. The control subjects had a 4.8-fold (95% confidence interval [CI] 2.2-10.3) increased risk of death compared with those who delivered after the diagnosis of breast cancer.

The major flaw of national cancer registry information is that only dates of diagnosis and death for both patients and control subjects were available, with no information on recurrence. It is likely that breast cancer patients who chose to become pregnant and give birth were disease free, as opposed to an unknown proportion of control subjects who may have had a recurrence at the time of matching but had not yet died. Thus, this bias may have contributed to control subjects having a poor survival rate and thereby making the cases appear to have a particularly good survival rate. The authors termed this bias a "healthy mother effect" to denote that tumor registry matching design chosen did not overcome the fact that women without recurrence were more likely to become pregnant.

The second published study is from the Stockholm Breast Cancer Study Group.¹⁹ This 1995 Swedish study also addressed the influence of subsequent pregnancy on breast cancer prognosis. The study population consisted of 2,119 women with primary operable breast cancer who were less than 50 years of age and were treated in the Stockholm region between 1971 and 1988. The study population was matched to the Stockholm County Council inpatient care registry — by computerized record linkage through use of the unique personal identification number — to obtain information about the patient's pregnancy history. A total of 50 pregnancies in 2,119 patients occurred after the diagnosis of breast cancer. The relative hazard adjusted for nodal status and age was 0.48 (95% CI 0.18-1.29) at a median follow-up of 7 years (range = 1-19 years). This was also the first study to report on estrogen receptor status, which was recorded in 70% of patients. The women with subsequent pregnancies had better survival rates if their cancer had positive estrogen receptors, which at first seems counterintuitive. However, this finding may be related to the fact that women with positive receptors have better survival rates and no micrometastatic disease.

The third of the population-based studies is from Denmark.²⁰ The study used computer linkage of the national records of Denmark on births, abortions, and breast cancer diagnosis. The authors identified 173 of 5,725 women with primary breast cancer aged 45 years or younger who became pregnant after treatment for breast cancer. Women who had a full-term pregnancy after treatment had a nonsignificantly reduced risk of dying (relative risk = 0.55, 95% CI 0.28-1.06) compared to women with no full-term pregnancy ($P=0.08$).

Unlike the Finnish study, the authors attempted to adjust for recurrence. Because virtually all women who undergo subsequent pregnancy are recurrence-free, the need for appropriate recurrence-free control subjects for matching is important but very difficult. In the Danish study, computer-matched linkage was accomplished for 93% of patients, and information on recurrence was available on 82% of them. However, it is unclear how carefully recurrence was sought and diagnosed. Furthermore, in an attempt to include as many pregnancies as possible, they entered cases up until 1994, and thus some had a limited follow-up of approximately one year. The population-based studies try to avoid the recollection bias prevalent in the retrospective studies, but they add biases perhaps in the choice of control subjects for the matching. These three studies add to the retrospective studies that show no detriment to subsequent pregnancy after breast cancer treatment. However, peculiar biases to each type of study exist. The Table is a summary of the studies on subsequent pregnancy.

Studies on Breast Cancer After Pregnancy				
Author	Year	Number of Patients	Study Period	10-Year Survival Node Negative/Positive
Harvey et al ¹³	1981	41	1940-70	80% / 79%
Ribiero et al ²³	1986	57	1941-80	64% / 26%
Mignot et al ¹⁴	1986	68	1940-85	90% / 71%
Ariel and Kempner ¹⁵	1989	46	1950-80	76% / 56%

Clark and Chua ¹⁶	1989	136	1931-85	64%
Sankila et al ¹⁸	1994	91	1967-89	93%
Von Schoultz et al ¹⁹	1995	50	1971-88	*
Kroman et al ²⁰	1997	173	1978-95	*
* 10-year survival not given.				

Future Studies and Advice to Current Patients

Only a study in which the patients are enrolled at diagnosis would provide comprehensive information on each patient at baseline, including clinical characteristics, treatment variables, and then a follow-up for medical status, recurrence, or any reproductive events. However, a prospective trial design is lengthy and expensive, with the goals obtained perhaps 10 years after its inception. The US Army, The University of Texas M.D. Anderson Cancer Center, Bowman Gray University, and Memorial Sloan-Kettering Cancer Center have launched a federally funded study accruing young women within eight months of diagnosis. Data are being collected on menstrual cycles, quality of life, and any reproductive events.²¹ The short-term goal is the study of premature menopause, addressing symptoms, and sexual dysfunction, and the long-term goal is to obtain information on subsequent pregnancies. No inpatient visits are necessary; all information is obtained by mail or telephone. The study intervention consists of medical record data, menstrual cycle diaries, and questionnaires.

Unfortunately, statistics on survival following subsequent pregnancy will not be forthcoming for several years. We currently tell our patients that there are reports of more than 1,000 women who have undergone subsequent pregnancy and appear to be doing well. We also comment that we do not believe that these studies are as conclusive as studies that deal with risk of recurrence, eg, those offering hormonal therapy or adjuvant chemotherapy for women with negative lymph nodes. Depending on the educational background of the patient, we discuss specific study design limitations: the anecdotal nature of the retrospective series in which the total population of those who had subsequent pregnancy is not known and the insufficient data available for choosing control subjects in the more recent population-based surveys.

After she is fully informed, the decision to become pregnant rests with the patient. Physicians are required to strike a balance between the uncertainty surrounding the safety of pregnancy and the need to restore a healthy and hopeful life, which for many young women includes childbearing. Other specific issues,²² such as interest in adoption, may also be part of the discussion with the patient.

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From the Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.

Address reprint requests to Jeanne A. Petrek, MD, at the Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY

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