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Research

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Pregnancy after breast cancer: population based study

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Abstract

Objectives To identify women who survived breast cancer and subsequently conceived and to determine the rate of pregnancy (proportion), management, outcome of the cancer, and outcome of the first subsequent pregnancy.
Design Population based descriptive study with cases identified from the Western Australian data linkage system and validated by review of medical charts. Supplementary data obtained from hospital and clinician records.
Setting Western Australia, 1982-2003.
Participants Women aged <45 with a diagnosis of breast cancer who subsequently conceived.
Main outcome measures Pregnancy outcome and rate, survival, time from diagnosis to pregnancy.
Results Sixty two (54%) women with a diagnosis of breast cancer who subsequently conceived did so less than two years after their diagnosis: 29 of them had an abortion, 27 had a live birth, and six miscarried. Within a proportional hazards regression model subsequent pregnancy was associated with improved overall survival (hazard ratio 0.59, 95% confidence interval 0.37 to 0.95). When the model was stratified by time from diagnosis subsequent pregnancy was associated with improved overall survival in women who waited at least 24 months to conceive (0.48, 0.27 to 0.83) and a non-significant protective effect was seen for women who waited at least six months to become pregnant.
Conclusions Our study does not support the current medical advice given to premenopausal women with a diagnosis of with breast cancer to wait two years before attempting to conceive. This recommendation may be valid for women who are receiving treatment or have systemic disease at diagnosis, but for women with localised disease early conception, six months after completing their treatment, is unlikely to reduce survival.

Introduction

For various reasons women of childbearing age with a diagnosis of breast cancer often want to conceive a child after treatment. Some might have delayed pregnancy until their 30s and 40s and now want a family. Little has been published regarding the management and outcomes of such women who subsequently conceive.[1–3]

Women with a diagnosis of breast cancer are often advised to wait at least two years after treatment before they attempt to conceive.[4 5] There are no published data to suggest that postponing conception will alter the outcome of the cancer or pregnancy. The two year wait is suggested as a guide and is based on anecdotal evidence. The delay is primarily to deter women who may develop early recurrence and to allow the completion of adjuvant therapies.[4 5]

Previous reports suggest that women who survive breast cancer and subsequently conceive have at least equivalent, if not better, survival than similar women matched for age and stage of cancer who do not subsequently conceive.[6–12] These findings imply that subsequent pregnancy may provide a survival benefit, possibly because of selection bias called the "healthy mother" effect.[13] This effect was first reported by Sankila et al in 1994 and suggests that women with a diagnosis of breast cancer who subsequently conceive are a self selecting group of women with better prognosis.[13]

Published research generally comes from small institution based studies and often identifies only live births.[14] Women who survive breast cancer may also miscarry or choose abortion so these results may not be representative of what happens when these events occur in a general population.[15]

We identified women who survived breast cancer and subsequently conceived in the Western Australian population in 1982-2003 and determined the pregnancy rate (proportion), management, and outcomes of the breast cancer and first subsequent pregnancy. We classified women with a diagnosis at age <45 as younger women.

Methods

We used the Western Australian data linkage system[16] to identify women with breast cancer in Western Australia who conceived at least once after their diagnosis of cancer. The system links 15 million health records and includes data from the hospital morbidity database, birth and death registries, mental health services, cancer registry, and midwives' notifications. The data are collected from the public and private health sectors for the Western Australian population and include records that date back to 1980.

We identified potential cases in two stages. Firstly, the linkage system identified women who were discharged from hospital with an international classification of diseases (ICD) code or a cancer or death registration for breast cancer (invasive or in situ) from 1 January 1982 to 31 December 2000. Age at diagnosis was restricted to 15-44 years. The ICD codes for breast cancer changed during the study period; episodes with a discharge date before 1 July 1999 were identified with ICD-9 or 9CM (codes 174.0-174.9 and 233.0). We used ICD-10AM (codes C50.0-C50.9 and D05.0-D05.9) from 1 July 1999. A de-identified version of this dataset was used for the analysis.[17 18]

Secondly, we used ICD diagnostic or procedure codes, or both, to identify women with a pregnancy subsequent to their diagnosis of breast cancer but before 31 December 2003. The outcome of the pregnancy could be abortion, miscarriage, ectopic, stillbirth, or live birth. The codes used included the procedure codes for dilatation and curettage, which in earlier versions of ICD combined both "diagnosis and treatment of

vaginal bleeding (any cause) and removal of products of conception (both miscarriage and abortion)."

We used pathology reports in the Western Australian cancer registry and hospital and clinician records to validate cases. A single experienced health researcher reviewed these records to obtain additional relevant data not available from the linkage system. The data collected included demographics, breast symptoms, method of diagnosis, management details (surgery, adjuvant therapy), characteristics of the tumour, management and outcome of subsequent pregnancy (including dates of last menstrual period, gestational age, and time from diagnosis of breast cancer to the estimated date of the last menstrual period), and overall survival.

A case was confirmed when we identified and validated a pregnancy after the first diagnosis of breast cancer. We excluded potential cases if the dilatation and curettage procedure was confirmed by pathology or operation report to be for diagnostic purposes only; the woman had undergone a sterilisation procedure such as a tubal ligation; and the breast cancer was diagnosed outside Western Australia (six cases).

Statistical analysis

We used SPSS 11.0 (release 11.0.1; SPSS, Chicago) for the descriptive analysis and included frequency, cross tabulations, χ^2 tests and Fisher's exact tests where applicable, and Kaplan Meier. Stata 9 (release 9, 2005; StataCorp, College Station, TX) was used for the Cox's proportional hazards regression model with a time dependent covariate. To calculate the time between diagnosis and first pregnancy, we designated the date of the first pathological diagnosis as the date of diagnosis and the date of the woman's last menstrual period as the date the pregnancy commenced (when this was unknown we estimated it by using the reported gestational age of the fetus at delivery). Overall survival was calculated and defined as the time from the date of diagnosis to the date of death or 31 December 2004.

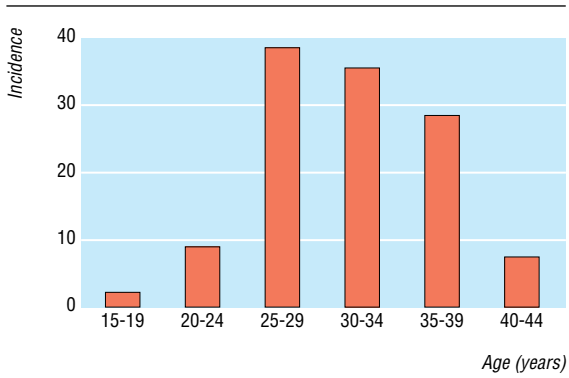
We used a proportional hazards regression model that included all women aged <45 with a pathological diagnosis of breast cancer during the study period, with subsequent pregnancy as the time dependent covariate. Subsequent pregnancy was coded as zero for all women until they become pregnant from which point they were coded as one. Variables in the model were age at diagnosis, tumour size, lymph node status, and time from diagnosis of cancer to approximate time of conception (<6 months, 6-24 months, and >24 months). As appropriate to the analysis, we calculated interquartile ranges or 95% confidence intervals and considered $P<0.05$ to be significant.

Results

In 1982-2000, 2539 women aged 15-44 in Western Australia had a pathologically confirmed diagnosis of breast cancer. Of these, 123 (5%) had at least one pregnancy after their diagnosis and before 31 December 2004.

The median age of the women who conceived after diagnosis was 31 (interquartile range 28-35) (figure). The median age at first subsequent pregnancy was 35 (31-38). Sixty seven (56%) women had naturally conceived at least one full term pregnancy before their diagnosis. The women who had a live birth after diagnosis were generally older than women in the general population who had a live birth (table 1).

In total, 175 subsequent pregnancies were confirmed in the 123 women; 45 (37%) women had more than one subsequent pregnancy. Sixty six (54%) women had a live birth (table 2). Three women successfully underwent in vitro fertilisation treatment to conceive after their diagnosis; at follow-up they were alive and without recurrence. The median time from diagnosis to first subsequent pregnancy was 23 months (interquartile range 11-42). There were no still births or ectopic pregnancies. Two births occurred before 36 weeks: a set of twins at 32 weeks after spontaneous rupture of membranes and a singleton birth by caesarean section at 30 weeks when the mother developed both local and distant metastases. All children were alive and well at last follow-up.



Age distribution of women with a diagnosis of breast cancer who subsequently conceived

Sixty two (50%) women conceived within two years of their diagnosis. Abortion was more common when conception occurred within two years of diagnosis ($P=0.012$) and proportionally more abortions occurred in the first six months after breast cancer was diagnosed and while the woman was undergoing active treatment (50% *v* 45%) (table 2). There was still a statistical difference in outcome of pregnancy between women who delayed conception two years and those who conceived within two years ($P=0.021$), even when we excluded women who conceived within six months of diagnosis (that is, during most adjuvant treatment) from the analysis.

Ninety five (77%) women had invasive ductal carcinoma. Tumour size ranged from 1 to 90 mm, with 58 (47%) tumours

Table 1 Age matched comparison of live births in women with a previous diagnosis of breast cancer and women in general population of Western Australia, 1983-2004. Figures are numbers (percentages) of women who conceived

Age (years)	With breast cancer	General population*
25-29	11 (16.7)	177 298 (47.1)
30-34	25 (37.9)	139 980 (37.1)
35-39	24 (36.4)	51 344 (13.6)
40-44	5 (7.5)	7917 (2.1)
≥45	1 (1.5)	325 (0.1)
Total	66	376 864

*For 1982-2003, from midwives notification system, Information, Collection and Management Branch, Western Australian Department of Health; 2006.

Table 2 Time from diagnosis of breast cancer to subsequent pregnancy and outcome of pregnancy. Figures are numbers of pregnancies (percentages)

Time to pregnancy	Full term	Miscarriage	Termination	Total
0-2 years*	27 (43)	6 (10)	29 (47)	62
0-6 months†	6 (30)	4 (20)	10 (50)	20
7-24 months†	21 (50)	2 (5)	19 (45)	42
>2 years	39 (64)	9 (15)	13 (21)	61
Total	66 (54)	15 (12)	42 (34)	123

*χ^2=8.870, 2df, P=0.012 Fisher's exact test—comparison for all pregnancy outcomes when conception before or after 24 months from diagnosis.
†χ^2=7.738, 2df, P=0.021 Fisher's exact test, when conceptions <6 months after diagnosis excluded.

Table 3 Characteristics of tumours in 123 women with a diagnosis of breast cancer

	No (%) of women
Type of carcinoma:	
Invasive ductal	95 (77)
Invasive lobular	7 (6)
In situ	6 (5)
Other	13 (11)
Unknown	2 (1)
Size (mm):	
<20	58 (47)
20-50	44 (36)
>50 mm	7 (6)
Unknown	14 (11)
Lymph node status:	
Negative	79 (64)
Positive	37 (30)
Unknown	7 (6)
Oestrogen receptor status:	
Negative	29 (24)
Positive	42 (34)
Unknown	52 (42)
Grade:	
I	14 (11)
II	28 (23)
III	46 (37)
Unknown	35 (28)
Stage of disease:	
In situ	6 (5)
Stage I	39 (32)
Stage II	65 (53)
Stage III	6 (5)
Unknown	7 (6)

<20 mm in diameter. Tumours were reported to be oestrogen receptor (ER) positive in 29 (24%) women (42% had unknown ER status), and 79 (64%) had unaffected lymph nodes. At diagnosis stage I (n=39, 32%) or stage II (n=65, 53%) were most common (table 3).

Most women had breast conserving surgery (n=70, 57%) (table 4). These women were more likely to have radiotherapy, though 12 women had breast conserving surgery alone as local management. Only seven (6%) women were confirmed to have started hormone therapy (tamoxifen). At least one woman taking tamoxifen conceived. She stopped taking tamoxifen when the pregnancy was discovered and the pregnancy resulted in a full term live birth. No women had ovarian suppression. Three women underwent ovarian tissue preservation before treatment but conceived naturally after adjuvant chemotherapy. Fifty women (41%) had chemotherapy. The most commonly administered regimen was cyclophosphamide, methotrexate, and fluorouracil (26, 21%). A further eight (7%) women received cyclophosphamide, methotrexate, and fluorouracil in combination with doxorubicin hydrochloride and cyclophosphamide. There was no difference in age between women who received chemotherapy and those who did not. Twenty six (52%) women who had chemotherapy did not wait two years to become pregnant.

One hundred and four (85%) women who had a pregnancy after cancer were reported to be alive with a median follow-up of 128 months (interquartile range 80-182). All the women who died in this study died from causes related to breast cancer. Disease recurred in 48 (39%) women, with a median overall time without recurrence of 42 months (interquartile range 20-75). The five year overall survival was 92% (95% confidence interval 87% to 97%), and 10 year overall survival was 86% (80% to 93%). Five year and ten year survival from first subsequent pregnancy was 87% (81% to 93%) and 85% (78% to 91%), respectively.

Table 4 Frequency of type of treatment in management of primary breast cancer. Figures are numbers (percentages)

Adjuvant treatment	Breast conserving surgery	Mastectomy	Total
None	9 (24)	28 (76)	37
Chemotherapy only	9 (38)	15 (62)	24
Radiotherapy only	24 (89)	3 (10)	27
Chemotherapy and radiotherapy	21 (81)	5 (19)	26
Unknown	7 (78)	2 (22)	9
Total	70 (57)	53 (43)	123

The Cox's proportional hazard regression model with subsequent pregnancy as a time dependent covariate showed that subsequent pregnancy improved overall survival (hazard ratio 0.59, 95% confidence interval 0.37 to 0.95, P=0.03) (table 5). When we stratified the proportional hazard regression model by time from diagnosis, subsequent pregnancy improved overall survival in those women who waited 24 months to become pregnant (0.48, 0.27 to 0.83, P=0.009). Pregnancy had a non-significant protective effect for all women who waited at least six months to become pregnant (table 6).

Discussion

Currently premenopausal women with a diagnosis of breast cancer are advised to wait two years before attempting to conceive. Our study does not support this, although the recommendation may be valid for women who are receiving treatment or have systemic disease at diagnosis. While some women will choose not to become pregnant after their diagnosis, an increasing number are likely to want the option of having children. For women with localised disease, early conception after completion of their breast cancer management is unlikely to adversely affect their survival.

Pregnancy rate

Diagnosis and treatment of breast cancer have a negative impact on reproductive opportunities for women of childbearing age. In our study the proportion of women who survived breast cancer and who conceived was lower than the proportion seen in the

Table 5 Cox's proportional hazards model for survival in women with breast cancer with time dependent variable

	β coefficient	P value	Hazard ratio (95% CI)
Age at diagnosis	–0.03	<0.001	0.97 (0.96 to 0.99)
Lymph node positive	0.96	<0.001	2.61 (2.17 to 3.13)
Tumour size (mm):			
<20			1.0
20-50	–0.49	<0.001	0.61 (0.50 to 0.75)
>50	0.05	0.592	1.05 (0.87 to 1.27)
Unknown	0.40	0.026	1.49 (1.05 to 2.10)
Subsequent pregnancy	–0.53	0.030	0.59 (0.37 to 0.95)

Table 6 Cox's proportional hazards model* for survival in women with breast cancer with time dependent variable stratified by time from diagnosis

Time to subsequent pregnancy (months)	β coefficient	P value	Hazard ratio (95% CI)
<6	0.79	0.579	2.20 (0.14 to 35.42)
6-24	–0.80	0.135	0.45 (0.16 to 1.28)
>24	–0.74	0.009	0.48 (0.27 to 0.83)

*Each stratified model adjusted for age, lymph node status, and tumour size.

general population. Women with breast cancer were more likely to have a live birth at a later age than seen in the general population because of the cancer treatment. The two year delay recommended after the end of treatment would further reduce the number of women who would conceive. We could not identify which women remained fertile after the diagnosis and therefore the pregnancy rate is a conservative estimate. The number of women who conceived in our study (123, 5%) was similar to the number reported in a Danish population based study, but some may have conceived after our cut-off date (31 December 2004).[3]

Pregnancy outcome

Sixty two (54%) women who subsequently conceived did so less than two years after their diagnosis, 29 of whom had abortions, including 10 in the first six months.

Anecdotal evidence suggests that there were four main reasons why women conceived within two years: they conceived between diagnosis and adjuvant treatment, when they were not aware that they would need chemotherapy and radiotherapy; advice on contraception was not given or not understood at the time of diagnosis; failure of a contraceptive method; and the desire to have a child above anything else.

It is concerning that women are becoming pregnant during adjuvant treatment. Some women who find they have conceived after diagnosis but before they start adjuvant treatment or who become "accidentally" pregnant while receiving adjuvant therapy may choose to have an abortion because of the increased risk of fetal malformation. Women who become pregnant anytime after treatment should be able to make their own informed choice about their pregnancy outcome.

Fertility

Only 50 women (41%) in this study had adjuvant chemotherapy, and seven (6%) had hormone therapy. The use of adjuvant chemotherapy did not affect the outcome of pregnancy in women who became pregnant at least six months after their diagnosis; more of these women had live births than had an abortion or miscarried. These outcomes were in similar proportions to those reported previously.[1 19] Hormone therapy was not available to women early in the study period, but even when it became available and was recommended many women chose not to take it.

To ask women to delay conception for two years after a diagnosis of breast cancer may allow the identification of those who relapse early and have a poor prognosis. For women with a good prognosis, however, adjuvant chemotherapy regimens may induce early menopause and at the least reduce ovarian reserve.[20] To delay conception for a further two years will probably lead to a further decline in already poor ovarian function and make pregnancy improbable, particularly for women diagnosed in their late 30s and early 40s. This has considerable clinical implications for the advice given to younger women with a diagnosis of breast cancer who have good prognostic markers and want the opportunity to conceive after treatment. Full counselling on the ramifications of conceiving and raising a child after treatment for a potentially life threatening disease should therefore be part of management for young women.

Survival

Overall survival at five (92%) and ten (86%) years was better for women who subsequently conceived than has been reported in similar cohorts.[1 7 12 21 22] This increased survival, while in part due to the "healthy mother" effect, could also be related to the improved management in breast cancer and increased survival seen for all women in Western Australia diagnosed during the time period.[23]

Women with breast cancer who conceived had improved survival compared with those who didn't conceive. When we accounted for time to pregnancy improved survival was significant only for women who waited at least 24 months to conceive. Clark and Chua also reported survival benefit for women when they delayed pregnancy for at least two years after diagnosis; these results were not adjusted for age, tumour size, or lymph node status.[1] In our study there was a definite protective effect for women who waited at least six months to conceive. We would expect that this result would become significant if more women conceived 6-24 months after treatment. The results reflect the clinical recommendation that women delay pregnancy for two years after diagnosis and suggest that women who have a good prognosis need not wait two years to become pregnant.

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Contributors: AI, CS, and JS were involved in the conception and design of the study and interpretation of the data. AI and MB undertook the data analysis. AI drafted the article and all authors revised and approved the final version. CS is guarantor.

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What is already known on this topic

Women who survive breast cancer and who conceive >24 months after diagnosis have similar or better survival than other women with breast cancer

Women are currently advised to wait at least two years after treatment for breast cancer before conception

Women with a diagnosis of breast cancer who have adjuvant chemotherapy may reduce their chance of later conceiving

What this study adds

For women with localised disease and good prognosis conception six months after treatment is unlikely to reduce survival

Pregnancy is unlikely to compromise the survival prospects for women treated for breast cancer who have tumours with good prognosis

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