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European Journal of Cancer 39 (2003) 736–741

European Journal of Cancer

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Review

# Pregnancy after breast cancer

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Received 9 September 2002; received in revised form 11 November 2002; accepted 16 December 2002

**Abstract**

The issue of pregnancy in patients previously treated for breast cancer is controversial. This paper reviews the literature using Medline and Embase databases over the last 50 years to address the issue. Overall survival in patients treated for breast cancer who subsequently become pregnant compares favourably with controls. This paper also addresses the effects of adjuvant therapy (loco-regional and systemic) on subsequent pregnancy. Introduction of a national registry of these patients may help inform such patients in the future.


*Keywords:* Pregnancy; Breast cancer

## 1. Introduction

Recent figures from the Office for National Statistics have shown that the average age of women at birth has gradually increased from 26.2 years in 1972 to 29.1 in 2000 [1]. With this shift, there may be a larger proportion of premenopausal patients with breast cancer who are yet to have a pregnancy in future decades. Only 6.5% of all breast cancers are diagnosed in women under 40 years and 21.8% diagnosed in those under 50 years [2]. Breast cancers in younger, premenopausal women are more likely to exhibit an adverse prognostic profile [3]. However, poorer survival previously seen in premenopausal women with breast cancer has improved with the use of better treatments in specialist centres by multidisciplinary teams [4]. It is therefore important to have an evidence base on which to provide information regarding the potential risks of pregnancy after a diagnosis of breast cancer.

This paper reviews the literature regarding the effect of a pregnancy subsequent to a diagnosis of breast cancer. It also assesses the influence of breast cancer treatment on subsequent pregnancies. Medline and Embase databases were searched to identify all published research between 1954 and 2002 relating to pregnancy after a diagnosis of breast cancer excluding all those regarding pregnancy-associated breast cancer. The literature regarding pregnancy in breast cancer survivors is limited to case series and case control studies. The primary outcome measure in the majority of these studies is survival.

## 2. Influence of subsequent pregnancy on survival

Many studies have shown that pregnancy following a diagnosis of breast cancer is not detrimental to survival. These studies are predominantly case control studies where cases are defined as women treated for breast cancer who subsequently become pregnant and controls are women treated for breast cancer who do not subsequently become pregnant. Population-based studies reporting relative risks are presented in Table 1. These studies have in fact shown that a subsequent pregnancy results in an improvement in survival with favourable relative risks of between 0.2 (0.1–0.5) [8] and 0.8 (0.3–2.3) [5]. The overall relative risk reported by Sankila and colleagues [8] is statistically significant. Cases and controls in this study were matched for age, stage of disease and year of breast cancer diagnosis, although this was done retrospectively and from registry data. When reported as 5- and 10-year survival rates in non-population-based studies, there still appears to be a survival advantage in those patients who become pregnant following a diagnosis of breast cancer. This is reported in both case control studies and case series (Table 2). This survival advantage is also observed in those with node-positive disease.

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0959-8049/03/$ - see front matter 
doi:10.1016/S0959-8049(02)00870-5

Table 1
Population-based studies reporting the influence of pregnancy in breast cancer survivors on survival

| Author [Ref.] | Year of publication | Year of study | Type of study | No. of cases | Relative risk of survival for exposed group (95% confidence interval) |
|---|---|---|---|---|---|
| Velentgas [5] | 1999 | 1983–1992 | Case control | 53 | 0.8 (0.3–2.3) |
| Kronman [6] | 1997 | 1978–1995 | Case control | 173 | 0.55 (0.28–1.06) |
| Von Schoulz [7] | 1995 | 1971–1988 | Case control | 50 | 0.42[a] (0.16–1.12) overall<br>0.48[a] (0.18–1.29) adjusted for nodal status |
| Sankila [8] | 1994 | 1967–1989 | Case control | 91 | 0.2 (0.1–0.5) |

[a] Relative hazard of distant metastasis.

Table 2
Non-population-based studies reporting 5- and 10-year survival rates in breast cancer survivors who had a subsequent pregnancy

| Author [Ref.] | Year of publication | Year of study | Type of study | No of cases | 5-year survival (%) node-negative | | 5-year survival (%) node-positive | | 10-year survival (%) node-negative | | 10-year survival (%) node-positive | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls |
| Gelber [9] | 2001 | NS | Case control | 94 | 92[a] | 85[a] | | | 86[a] | 74[a] | | |
| Malamos [10] | 1996 | 1978–1995 | Case control | 21 | | | | | | | | |
| Lethaby [11] | 1996 | 1976–1985 | Case control | 14 | 100 | 80 | 50 | 50 | | | | |
| Sankila 8] | 1994 | 1967–1989 | Case control | 91 | 96 | 77 | 79 | 49 | 96 | 67 | 79 | 42 |
| Dow [12] | 1994 | 1968–1985 | Case control | 23 | NS | | | | | | | |
| Aerial [13] | 1989 | 1950–1980 | Case series | 46 | | | | | 77 | | 56 | |
| Clark [14] | 1989 | 1931–1985 | Case series | 136 | | | | | 76 | N/A | 63 | N/A |
| Ribiero [15] | 1986 | 1941–1980 | Case series | 57 | 64 | | 30 | | 64 | | 26 | |
| Harvey [16] | 1981 | 1940–1970 | Case series | 41 | NS | NS | NS | NS | 80 | N/A | 79 | N/A |
| Cheek [17] | 1973 | NS | Case series | 10 | 50 | | | | | | | |
| Cooper [18] | 1970 | NS | Case control | 32 | 94 | 71 | 45 | 45 | | | | |
| Rissanen [19] | 1969 | 1936–1959 | Case series | 53 | 77[a] | | | | 70* | | | |
| Holleb [20] | 1962 | 1920–1953 | Case series | 52 | 64 | | 38 | | | | | |
| White [21] | 1955 | 1850–1953 | Case series | 269 | 64.6 | | 43.8 | | 51 | | 34.6 | |
| White [22] | 1954 | NS | Case series | 208 | 49[a] | | 16.8[a] | | | | | |

NS, not stated; NA, not applicable.
[a] Overall survival for node-negative and node-positive disease.

Several authors have previously reviewed the literature regarding pregnancy following a diagnosis of breast cancer [21,23–26]. Danforth and colleagues [23] reached certain conclusions: they found that pregnancy does not affect the prognosis of patients with stage 1 or 2 breast cancer and based on the data reviewed, advised waiting until 2 years postsurgery prior to conception. Petrek [24] reported that ''the effect of a subsequent pregnancy on breast cancer prognosis is uncertain because the patients on which we have reports probably represent a small and selectively obtained group of patients from any institution''.

Subsequent to these reviews, further publications have not altered these findings. Several factors within these studies and the populations included make the interpretation and comparison of data reported complex. The influence of subsequent pregnancy on breast cancer survival remains a controversial issue. Studies published on this subject are based on few cases and bias remains prevalent in the analyses.

## 3. Influence of pregnancy on recurrence and distant metastasis

Other outcome measures include recurrence and incidence of distant metatasis. However, the lack of data is due to the fact that the studies are retrospective with incomplete data. Malamos and colleagues [10] present a rate of local recurrence of 14% in the pregnant group and 39% in the non-pregnant group. Sutton and colleagues [27] in 1989 also reported a recurrence rate of 28% in the pregnancy group and 46% in the non-pregnant group. In these studies, however, the site of recurrence is not clearly defined. Conversely, Von Schoulz and colleagues [7] using registry data reported a 24% rate of distant metastasis in the pregnant group compared with 8% in the non-pregnant group.

From the above, it is appears that pregnancy may not have a detrimental effect on survival or distant metastasis in patients previously treated for breast cancer.

This may be a real effect although other factors have to be considered.

## 4. 'Healthy mother effect' [8]

Interpretation of data can also be problematic due to the population under study.

Women who become pregnant following treatment for breast cancer are thought to have different characteristics to women who do not become pregnant. This results in a 'healthy mother' bias: those who feel well have children and those who are affected by the disease do not [8]. Sankila and colleagues suggest that even when cases and controls are matched at the time of diagnosis, their prognosis may not be the same at the time of pregnancy or delivery. It is suggested that to assess the actual effects of pregnancy on survival, the patients should be matched at delivery [8]. This would reduce confounding by tumour variables in analyses. Collection of data regarding prognostic variables at the time of pregnancy, however, would be limited in retrospective studies.

There is also difficulty in controlling for known risk factors in the statistical models used, as data is often incomplete with these retrospective studies. For example oestrogen receptor status is often unrecorded in up to 50% of patients [12], with factors such as family history and previous parity unknown. It appears from studies [5,8] that patients becoming pregnant after a diagnosis of breast cancer are younger than controls and less likely to have had a pregnancy prior to diagnosis. To allow for the many factors which could be confounders in these studies, controls are matched to cases predominantly on the basis of age and tumour stage.

## 5. Methodology of studies

Studies of pregnancy after breast cancer are predominantly retrospective case control studies or case series. This introduces a number of issues regarding methodology. The denominator population of women undergoing pregnancy does not always include all those who become pregnant due to the difficulty in identifying cases in retrospective studies. The definition of 'pregnancy' also varies between studies with some using all pregnancies as a baseline including those that result in a spontaneous abortion [7] whilst others only include those that result in a full-term pregnancy [8]. There will also be recall bias in terms of pregnancies which end, for example, in miscarriage. It is therefore claimed that the denominator population of those becoming pregnant after breast cancer is an underestimate and that it may only represent 10% of the population becoming pregnant after treatment for breast cancer [24].

Population-based studies show a higher incidence of pregnancy postbreast cancer treatment. Velentgas and colleagues [5] reported 53 pregnancies amongst 618 cases of breast cancer in women under 40 years (an incidence of 8.6%), diagnosed between 1983 and 1992 with stage 1 or 2 disease. These patients were identified through the Cancer Surveillance System population-based registry. However, attrition of the original cohort of this registry had occurred due to death or illness resulting in a subsequent cohort which was therefore not representative. This may cause bias in the subsequent analyses. This incidence rate of pregnancy following breast cancer varies between studies probably because of different methods of collecting data regarding pregnancy, for example, the use of birth registry data or retrospective assessment of hospital notes. In addition, the incidence of pregnancy will depend on the age definitions. In a study by Kronman [6], 26% of those with live births were in the age group greater than 35 years. In a study by Clark and Chua [14] 12.5% of those with pregnancy after breast cancer were older than 40 years at the time of their pregnancy. Therefore, by imposing strict age criteria rather than all those who become pregnant, a proportion of patients may be excluded.

## 6. Length of time from diagnosis of breast cancer to pregnancy

When looking at the length of time from diagnosis of breast cancer to pregnancy and whether this affects survival, it is again difficult as the numbers are small and stratifying for different time bands makes the analysis less valid. Clark and Reid [28] found that survival was better with a longer time interval between cancer diagnosis and conception. They reported a 5-year survival rate of 54% in those who became pregnant within 6 months of a diagnosis and 78% in those who waited between 6 months and 2 years. This trend was also reported by Clark and Chua who found a 92% survival rate at 5 years for those with an interval of 2 years and 59% for those with a 6-month interval [14]. Sankila and colleagues [8] found this not to be the case. For an interval from diagnosis to delivery of 10–24 months, the relative risk for controls was 11.3 (1.6–82.8) and for 25–60 months, the relative risk for controls was 2.6 (1.1–6.0). Gelber and colleagues [9] reported a better survival rate in those who had a subsequent pregnancy (5-year survival of 92% versus 85% in cases versus controls, respectively), even though 43% of cases completed a pregnancy within 2 years of diagnosis. The definition of this time interval is variable. Some studies use the length from time of diagnosis to time of delivery which then excludes abortions, whilst others use time from diagnosis of breast cancer to diagnosis of pregnancy which will then include all pregnancies.

## 7. Hypothesis regarding survival

The survival advantage for those patients who become pregnant subsequent to a diagnosis of breast cancer may in part be due to the bias of retrospective studies. A foetal antigen hypothesis has, however, been proposed [29] to account for a causal effect of pregnancy on survival of women who have had a diagnosis of breast cancer. This suggests that during pregnancy, isoimmunisation occurs due to breast carcinoma cells and foetal cells sharing common antigens. It is postulated that foetal antigens raised during pregnancy can elicit a memory response through the immune system and that this can therefore prevent the development of further disease through an immune response to subclinical micrometastases [30]. Further studies have supported this hypothesis by confirming the presence of a tumour-specific antigen, MUC1, on both foetal and breast cancer tissues [31].

## 8. Influence of adjuvant treatment on subsequent pregnancy

### 8.1. Effect of chemotherapy on ovarian function

Chemotherapeutic agents affect follicular growth and maturation resulting in ovarian failure. This results in irregular menses and amenorrhoea. Cyclophosphamide causes fibrosis of ova causing a reduction in oestrogen and disruption of the normal menstrual cycle. Methotrexate and 5-fluorouracil also induce amenorrhoea. However, the effects of other agents including doxorubicin and anthracyclines are unclear. Alkylating agents are more likely to cause infertility than non-alkylating agents [32]. The risk of developing treatment-induced ovarian failure is dependent on age and the total cumulative dose of a drug, with older patients showing greater susceptibility [33].

Bonadonna and colleagues [34] showed that 54% of 549 menstruating women under the age of 40 years had amenorrhoea following treatment with cyclophosphamide, methotrexate, 5-fluorouracil (CMF). In women older than 40 years, the incidence was 96%. Dinistrian and colleagues [35] showed that patients 40 years and older developed amenorrhoea within 2–4 months of treatment. This was in comparison to 2 patients in their study under 30 years who showed no evidence of ovarian suppression 2 years after therapy. Koyama and colleagues [36] showed that only 5.2 g of an average cumulative oral dose of cyclophosphamide was needed to induce amenorrhoea in 13 patients aged 40–48 years (mean 44.6 years), 9.3 g in 5 patients aged 33–38 years (mean 36.6 years) and 20.4 g in 5 patients aged 22–29 years (mean 25.4 years). Approximately 50% of women less than 35 years resumed normal menses following completion of chemotherapy. Sutton and colleagues [27] reported 33 pregnancies in 25 patients resulting in 19 offspring. They showed that a sizeable proportion of these women retained ovarian function. The median interval between chemotherapy and pregnancy was 12 months range 0–87 months. They also reported that of 128 menstruating women, only 9% experienced permanent amenorrhoea following chemotherapy.

### 8.2. Effect of radiotherapy

One of the most comprehensive studies providing information on the effect of radiotherapy was that carried out by the Joint Centre for Radiation Therapy in Boston [12]. The health records of 1624 patients who were treated at the centre between 1968 and 1985 were examined. 23 patients who had subsequent pregnancies were matched with women who had no pregnancies. They were matched for age, stage at diagnosis and time to pregnancy without recurrence. 22 of 23 women who had pregnancies went on to deliver normal full-term babies. The remaining patient delivered a low birthweight infant. The mean time to pregnancy was 30 months (range 6–84 months). Their findings matched previous studies demonstrating no adverse clinical outcome on pregnancy subsequent to surgery or radiotherapy. Malamos and colleagues [10] also showed no consequence of radiotherapy treatment on the rate of pregnancy. In addition, at a mean follow-up of 38 months no anatomical defects were observed in the offspring. Both studies showed no added risk for recurrent disease or death from breast cancer.

Dow and colleagues [12] reported diminished lactation from the irradiated breast in those women who had undergone radiotherapy following breast-conserving surgery. The average radiation dose was 4600 cGy, which presumably caused atrophy of the breast lobules. Higgins and colleagues reported a series of 13 patients in which 1 patient successfully breast fed following surgery and radiotherapy and 3 further patients lactated from the treated breast, but were unable to breast feed [37].

## 9. Teratogenicity of adjuvant systemic therapy

The incidence of teratogenesis in the general population is 3%. Little is known about foetal outcome following treatment of a pregnant patient with tamoxifen. However, adverse effects of tamoxifen in animal studies have been demonstrated [38]. With regard to chemotherapy, Doll and colleagues [39] have shown that if chemotherapy is administered during pregnancy, there is a 16% incidence of foetal malformation if used in the first trimester, but no increase in the incidence of teratogenesis if therapy is commenced in the second or third trimester. The incidence in the first trimester was

reduced to 6% if folate antagonists were used in combination with chemotherapy. However, the delayed effects of chemotherapy on offspring is unknown, on those conceived either whilst the mother is undergoing chemotherapy treatment or subsequently. It is therefore suggested that registry data for these women and their offspring is required [33].

## 10. Quality of life (QOL)

There have been few qualitative studies on a women's adjustment to breast cancer and, as a result, little understanding of the concerns of younger women following a diagnosis of breast cancer [40]. Few papers assess quality of life with regard to a subsequent pregnancy. Dow [12] states that in addition to prognostic indicators after breast cancer, perceived quality of life, desire for children and the degree of support for or from one's spouse and family were also highly important considerations in deciding to have children after breast cancer.

A QOL questionnaire survey of patients by Dow and colleagues [12] reported that women having children after breast cancer reported that family issues provided the greatest degree of satisfaction and importance to quality of life. Scores between cases and controls were comparable. They also measured parent stress, through the parenting stress index, in those with a subsequent pregnancy. It was found overall that women having children after breast cancer had similar and not excess levels of stressors in the parent–child system compared with the normative group.

## 11. Conclusion

Based on available data, the effect of a subsequent pregnancy on patients who have had breast cancer with regard to local recurrence, distant metastasis and survival remains debatable. Current evidence is difficult to interpret due to differing populations and the techniques of data collection. Only large prospective studies may answer these questions. Within prospective studies, analysis using a nested case control approach could be used. Until these data are available, advice to women regarding subsequent pregnancy has to be based on the evidence in the literature and individual patient circumstances. It is also recommended that a national registry of such patients be introduced which will provide information in order to advise patients in the future.

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