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OVERALL SURVIVAL FROM BREAST CANCER IN WOMEN PREGNANT OR LACTATING AT OR AFTER DIAGNOSIS

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The effect of concurrent or subsequent pregnancy or lactation has been studied in women with breast cancer to determine if these variables influence prognosis. Information was collected from 382 women potentially capable of bearing children, aged less than 45 years, in the Auckland Breast Cancer Study Group data file, a consecutive series of women diagnosed with breast cancer from 1976 to 1985, with a median follow-up of 10.2 years. The prevalence of both pregnancy at diagnosis and lactation at diagnosis was 2.6%. The incidence of pregnancy subsequent to diagnosis was 3.9%. Women pregnant at the time of breast cancer diagnosis had significantly more advanced disease than non-pregnant patients, and there was a similar trend for women lactating at diagnosis. Overall survival in these women was poor compared with the non-pregnant and non-lactating groups; only 2 of 10 pregnant patients and 0 of 10 lactating patients survived more than 12 years. The adverse outcome for women lactating at diagnosis of their breast cancer persisted despite allowance for nodal status, tumour size and age. However, survival was similar between pregnant and non-pregnant patients when these variables were taken into account. No significant differences in survival were found between those women who had pregnancies subsequent to diagnosis of breast cancer and breast cancer patients who did not become pregnant.

Breast cancer associated with pregnancy has traditionally been thought to confer a poor prognosis. Late last century, Samuel Gross suggested that when breast cancer was associated with pregnancy, "its growth was wonderfully rapid and its course excessively malignant" (Treves and Hellab, 1958). Haagenson and Stout (1943) noted the poor prognosis of 20 pregnant patients treated for breast cancer and concluded that no patients with breast cancer diagnosed during pregnancy should undergo surgery because they were incurable. This attitude has moderated in recent years, though there is a lack of consensus among clinicians over the management strategy of breast cancer during pregnancy, with a suspicion that gestational breast cancer is possibly a different and more aggressive disease from that seen in non-pregnant women. These concerns also affect advice to young women with a history of a previous breast cancer who wish to become pregnant.

This report investigates the prevalence, characteristics and outcome of breast cancer patients less than 45 years of age in the Auckland region between 1976 and 1985, who were either pregnant or lactating at diagnosis or who undertook a pregnancy subsequent to breast cancer detection.

METHODS

Patients

From 1976 to 1985, 2,706 women were diagnosed with breast cancer in the greater Auckland region. Case ascertainment was by comprehensive review of all breast histopathology reports from public and private histopathology services and was double-checked against cancer registry files; it is considered that case ascertainment was virtually complete (Newman *et al.*, 1992). Data on these patients and their subsequent follow-up have been recorded on a computerised data file, and by August 1993, the median duration of follow-up was 10.2 years.

Methods

A routine follow-up questionnaire, with questions pertaining to pregnancy or lactation at diagnosis and subsequent pregnancy and lactation, was sent to the family practitioners of all patients aged less than 45 years at diagnosis. Additional information was obtained from hospital notes in some cases. Data requested included pregnancy and lactation status at breast cancer diagnosis together with pregnancy and lactation status and number of live births after breast cancer diagnosis. "Pregnancy status at diagnosis" and "lactation status at diagnosis" were defined as pregnant or breast-feeding at or within 3 months of histological confirmation of breast cancer.

Fisher's exact test was used to test for differences in the distributions of variables, and survival analysis was performed using the Kaplan-Meier product limit estimate method, with the log-rank statistic being used to test for differences between groups. Cox's proportional hazards model was used to assess independent effects.

RESULTS

Of the total data file of 2,706 patients, 445 (16% of the total) were aged less than 45 years at diagnosis of breast cancer. Information on pregnancy status at diagnosis and subsequent pregnancies was available for 430 (97%) and 405 (94%), respectively, of the eligible group. Careful examination of the characteristics of cases with missing information (n = 15) compared with the studied cases (n = 430) confirmed that there was no obvious bias between these groups, both showing a similar distribution of age, nodal status and tumour size (data not shown).

Of the 2 total eligible groups, 48 had a history of sterilisation (hysterectomy or tubal ligation), leaving 382 potentially capable of bearing children at the time of their breast cancer diagnosis and 357 who were able to have a subsequent pregnancy. The prevalence of both pregnancy at diagnosis and lactation at diagnosis was 2.6%. The incidence of pregnancy after diagnosis was 3.9%.

Of the 10 women who were pregnant at breast cancer diagnosis, the majority (70%) were Maori and Pacific Island Polynesian compared with 14% in the non-pregnant group. The median age of the women pregnant at diagnosis was 33 years, which compares with a mean age of 40 years in the non-pregnant group. All but 3 of the 10 pregnant women were node-positive (70%), and the majority (60%) had tumours greater than 5 cm. Chi square analysis confirmed that the distributions of nodal status and tumour size were significantly different from those of the group of women who were not pregnant at diagnosis (Table I), with the pregnant group having larger tumours and being more likely to be node-positive. The median delay from first sign or symptom to diagnosis was similar in both the pregnant and non-pregnant

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groups. A disproportionate number in the pregnant group had grade 3 tumours and oestrogen receptor–negative status. All but 2 of the women had live births and have since died, at a median interval of 2 years (range 1 year 1 month–8 years 8 months) after diagnosis. The 2 women currently alive had incomplete pregnancies with gestations of 4 and 6 weeks. The remaining cases developed recurrence before death, with a median disease-free interval of 1 year (range 0–6 years 8 months).

The majority (80%) of the women breast-feeding at the time of breast cancer diagnosis were European and the remainder, Maori. The median age of these women was 31 years. The majority (80%) were node-positive, 1 woman was node-negative and nodal status was not investigated in 1 woman. Chi square analysis confirmed that significantly more women breast-feeding at diagnosis were node-positive than those not breast-feeding (Table II). The median delay from first sign or symptom to diagnosis did not differ in the breast-feeding and non-breast-feeding groups. Where receptor status was recorded, the majority of breast-feeding patients were receptor-negative. A comparison of tumour size showed a similar distribution to those women not breast-feeding at diagnosis. All of the 10 women in this group have subsequently died, with a median disease-free interval of 1 year 8 months (1 month–2 years 5 months) and a median interval to time of death of 3 years 4 months (1 year 1 month–12 years 1 month).

Of the 14 women who became pregnant subsequent to diagnosis, 50% were European compared with 85% in the non-pregnant group. The median age of this group of women at breast cancer diagnosis was 27 years 6 months (15–42 years) and the median interval between breast cancer diagnosis and pregnancy was 2 years 3 months (5 months–7 years 5 months). Ten women (71%) were node-negative and 4 (29%) were node-positive. None had metastases at presentation. One woman, pregnant at diagnosis with subsequent miscarriage, had 2 further pregnancies and is alive at 11 years of follow-up. Nine of the 14 women in the subsequent pregnancy group were alive and well at last follow-up (detailed tables of the individual characteristics of patients pregnant or lactating at diagnosis or pregnant subsequent to diagnosis can be obtained from the authors upon request).

Direct comparison of survival curves for women pregnant or non-pregnant at diagnosis suggests an overall advantage for those not pregnant at diagnosis (Fig. 1). However, as noted, there is a strong imbalance in nodal status, size of tumour and age between the 2 groups. Cox's regression, with these prognostic factors in the model, confirmed that while pregnancy status initially influenced outcome after breast cancer diagnosis, the effect was no longer significant after adjusting for nodal status, tumour size and age (Table III).

Comparison of the group of women breast-feeding with the group not breast-feeding at diagnosis showed a pattern similar to the pregnancy patients. Overall, the breast-feeding group had significantly poorer survival than the non-breast-feeding group (Fig. 2), and breast-feeding status at diagnosis continued to significantly influence survival in Cox's regression model independent of nodal status, tumour size and age (Table IV).

Women who undertook pregnancy subsequent to diagnosis and treatment of breast cancer were matched for survival with non-pregnant patients according to nodal status to adjust for potential imbalances between the 2 groups (Fig. 3). There was no significant difference between either the 2 groups of node-positive women or the 2 groups of node-negative women. Time-dependent analysis with Cox's regression, controlling for age, nodal status and size of tumour, also indicated no evidence of an effect of subsequent pregnancy on outcome.

TABLE Ia – DISTRIBUTION OF NODAL STATUS BY PREGNANCY STATUS AT DIAGNOSIS

	Pregnant at diagnosis		Not pregnant at diagnosis	
	n	%	n	%
Node-negative	3	(30)	216	(63)
Node-positive	7	(70)	129	(37)

$\chi^2 = 4.37$, Fisher's exact test (1-tailed), $p = 0.04$.

TABLE Ib – DISTRIBUTION OF TUMOUR SIZE BY PREGNANCY STATUS AT DIAGNOSIS

	Pregnant at diagnosis		Not pregnant at diagnosis	
	n	%	n	%
Tumour size				
≤2 cm	1	(10)	185	(45)
>2 cm	9	(90)	230	(55)

$\chi^2 = 4.74$, Fisher's exact test (1-tailed), $p = 0.03$.

TABLE II – DISTRIBUTION OF NODAL STATUS BY LACTATION STATUS AT DIAGNOSIS

	Lactating at diagnosis			
	No		Yes	
	n	%	n	%
Node-negative	218	(63)	1	(11)
Node-positive	127	(37)	8	(89)

$\chi^2 = 10.08$, Fisher's exact test (1-tailed), $p = 0.002$.

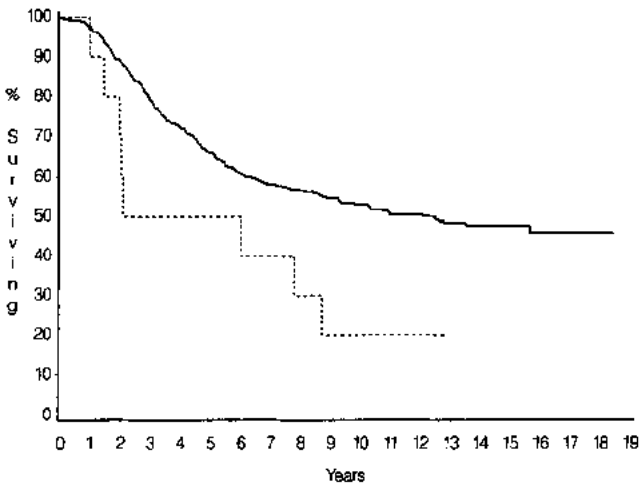

FIGURE 1 – Overall survival by pregnancy status at diagnosis in women <45 years of age (n = 430, $p = 0.02$, log-rank): ——— not pregnant at diagnosis (n = 420, died = 200), - - - - - pregnant at diagnosis (n = 10, died = 8).

TABLE III – COX'S PROPORTIONAL HAZARD MODEL FOR OVERALL SURVIVAL IN WOMEN WITH BREAST CANCER, <45 YEARS OF AGE

Single variables	χ^2 score	p
Pregnant at diagnosis	11.7	0.0006
Nodal status	47.1	<0.0001
Tumour size	31.2	<0.0001
Age (yr)	4.3	0.04

Multivariate analysis	Wald χ^2	p	Risk ratio
Nodal status	40.50	<0.0001	2.82
Tumour size	22.10	<0.0001	1.82
Age (yr)	7.68	0.0056	0.96

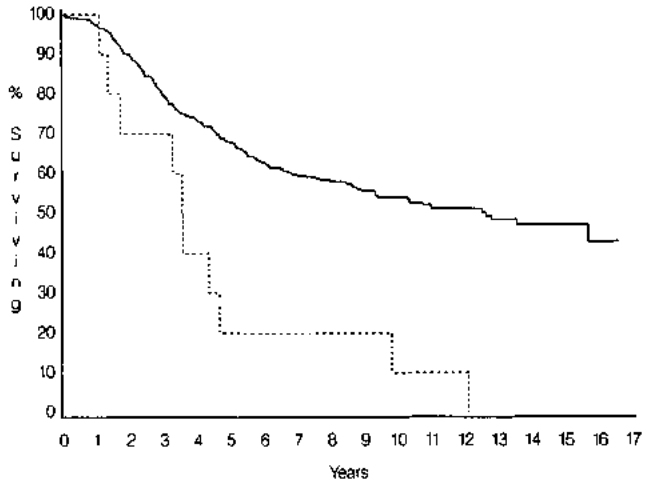

FIGURE 2 – Overall survival by lactation status at diagnosis in women <45 years of age (n = 421, $p < 0.0001$, log-rank): ——— not lactating at diagnosis (n = 411, died = 190), - - - - - lactating at diagnosis (n = 10, died = 10).

TABLE IV – COX'S PROPORTIONAL HAZARD MODEL FOR OVERALL SURVIVAL IN WOMEN WITH BREAST CANCER, <45 YEARS OF AGE

Single variables	χ^2 score		p
Breast-feeding at diagnosis	12.8		0.0003
Nodal status	47.3		<0.0001
Tumour size	27.3		<0.0001
Age (yr)	4.3		0.04
Multivariate analysis	**Wald χ^2**	**p**	**Risk ratio**
Nodal status	34.26	<0.0001	2.7
Tumour size	20.05	<0.0001	1.8
Breastfeeding at diagnosis	5.21	0.0225	2.3
Age (yr)	5.07	0.0244	0.96

though there was a trend towards more favourable prognosis in the pregnancy group (Table V).

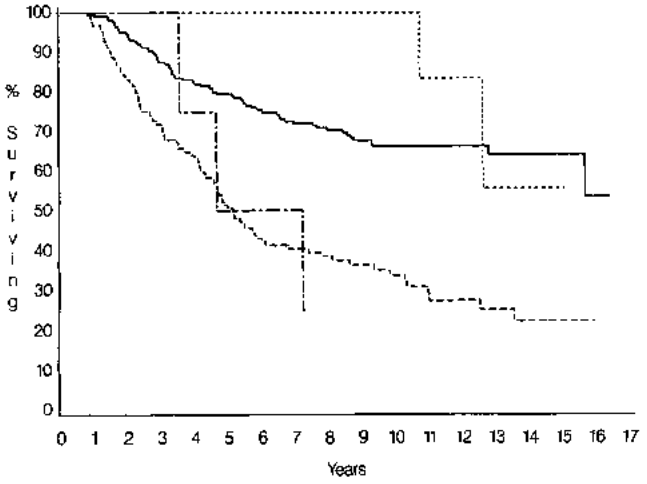

FIGURE 3 – Overall survival by pregnancy status subsequent to breast cancer diagnosis in women <45 years of age: ——— node-negative, no later pregnancy (n = 207, died = 68), - - - - - node-negative, later pregnancy (n = 10, died = 2), — — — node-positive, no later pregnancy (n = 127, died = 85), — - — - node-positive, later pregnancy (n = 4, died = 3).

TABLE V – COX'S PROPORTIONAL HAZARD MODEL FOR OVERALL SURVIVAL IN WOMEN WITH BREAST CANCER, <45 YEARS OF AGE

Single variables		χ^2 score	p
Subsequent pregnancy[1]		0.15	0.70
Nodal status		42.87	<0.0001
Tumour size		24.64	<0.0001
Age (yr)		2.15	0.14
Multivariate analysis	**Wald χ^2**	**p**	**Risk ratio**
Nodal status	34.62	<0.0001	2.69
Tumour size	17.30	<0.0001	1.78
Age (yr)	3.28	0.07	0.97

[1]At model termination, the χ^2 score for subsequent pregnancy was 2.71, $p = 0.099$.

DISCUSSION

Pregnancy or lactation at breast cancer diagnosis

"Pregnancy-associated breast cancer" is frequently defined as breast cancer diagnosed simultaneously or within 1 year after pregnancy (Petrek *et al.*, 1991). In the present study, a more conservative definition was adopted; thus, the prevalence estimates were less than those previously reported (Treves and Hellab, 1958; Greene, 1988). When the group of women pregnant at diagnosis was combined with the group lactating at diagnosis, to approximate the Petrek *et al.* (1991) definition, the prevalence of "pregnancy-associated" breast cancer in women aged less than 45 years was 5.2%, which is closer to previous estimates. In addition, the number of patients identified in the present study who had undergone sterilising procedures may have been an underestimate, also affecting the assessment of true prevalence. By comparison, Petrek (1991) reported a 15% incidence of pregnancy among breast cancer patients less than 40 years of age. Moreover, there may be a considerable number of pregnant patients with sub-clinical breast cancer. Given the prolonged pre-clinical growth phase of breast tumours based on the current knowledge of growth rates (Moolgavkar *et al.*, 1980), cancers diagnosed some years after a delivery may have co-existed with the pregnancy.

The majority of studies are consistent with the present findings that women with pregnancy-associated breast cancer present with more advanced disease, especially in terms of lymph node status, than those who are not pregnant (Petrek *et al.*, 1991; Peters, 1968; King *et al.*, 1985; Ribeiro *et al.*, 1986). A number of possible explanations have been proposed, including delay in diagnosis (Gallenberg and Loprinzi, 1989; Nugent and O'Connell, 1985), difficulties in tumour detection in those with breast engorgement and hypertrophy and medical attention diverted to the pregnancy rather than routine health checks. In this study, comparison of the group pregnant at diagnosis with the non-pregnant group indicates that the former had more advanced disease (as measured by nodal status and size of tumour) and were younger, both of these factors being associated with a worse prognosis (Carter *et al.*, 1989; Lethaby *et al.*, 1992). Delay in seeking treatment did not appear to be an issue since the time interval between first signs and symptoms and definitive breast cancer diagnosis did not differ significantly between the pregnant or lactating groups and the non-pregnant and non-lactating groups.

It is difficult to determine whether the disproportionate distribution of ethnicity in the pregnant group is a significant finding. However, we have noted in an earlier report that Pacific Island and Maori women are more likely to present with advanced disease than European women (Newman *et al.*, 1992).

It is possible that differences in treatment regimes between those pregnant and those not pregnant at breast cancer

diagnosis may have influenced these results. However, there is no evidence for this from a review of case notes and no evidence of a delay in starting recommended treatment in the pregnant group.

The view that concurrent breast cancer and pregnancy/lactation has a poor prognosis has been challenged by more recent studies which have controlled for stage at presentation and age (King *et al.*, 1985; Nugent and O'Connell, 1985; Greene, 1988; Zemlickis *et al.*, 1992). Nugent and O'Connell (1985) have suggested that age rather than pregnancy may be the major negative prognostic factor in these patients. Their results showed no difference in survival for pregnant patients compared with matched controls of the same age, whereas when those under 40 were compared with patients over 40 years old, there was a significant decrease in 5-year survival in the younger group. Other studies have not used age-matched controls, though Tretli *et al.* (1988) in a study of 20 breast cancer patients diagnosed during pregnancy found a significantly poorer prognosis for these women after taking stage of disease, age and calendar year at diagnosis into account.

Our data confirm the results found in the majority of recent studies. The women in the pregnant group presented with more advanced disease, which had a significant effect on their prognosis, but their adverse outcome could be adequately explained by nodal status, tumour size and age. This result persisted when the 2 women who had incomplete pregnancies, with a much smaller time interval of increased hormonal stimulation, were removed from the analysis. However, the significant adverse effect on prognosis of breast-feeding at diagnosis could not be explained by imbalances in the extent of disease in the breast-feeding and non-breast-feeding groups. Women lactating at breast cancer diagnosis had a poorer outcome compared to women not lactating. The reason for the discrepancy between the effects of the pregnancy and lactation groups on prognosis is not certain, but the issue could be clarified in a larger study. Moreover, the reason for the more advanced stage of tumour in both groups at presentation is unclear. However, since the prognosis of patients with node-positive disease and large tumours is poor, concurrent pregnancy or lactation *per se* may be a poor prognostic marker for women with breast cancer (Clark and Chua, 1989).

Subsequent pregnancy

The incidence of subsequent pregnancy in this investigation is similar to the incidence of 7% in breast cancer patients less than 40 years old found by Petrek (1994). By comparison, most other retrospective studies that have assessed the effect of subsequent pregnancy on prognosis have reported on a smaller proportion of patients. It is likely that many of these reports have emphasized patients who have done well (Petrek, 1994).

In our study, women undergoing a subsequent pregnancy did not appear to differ markedly from the group with no subsequent pregnancies in terms of outcome, though most were younger than the non-pregnant patients. There was a trend towards less advanced disease in this group, but this could reflect selection bias since many women would avoid pregnancy if their perceived risk of recurrence was high.

There is no consensus concerning the effect of a subsequent pregnancy on breast cancer prognosis, and conclusions must be regarded with caution due to data collection problems. Most oncologists accept that a small residuum of cancer in the non-pregnant patient may be kept in check by host defence mechanisms. There is concern that these mechanisms may be decreased in concurrent pregnancy, prompting many clinicians to recommend against conception in those with previous breast cancer. In practice, however, it has generally been observed that breast cancer patients who subsequently become pregnant have either unaltered survival or even a survival advantage, and this has been demonstrated in both age- and stage-matched groups (Donegan, 1972; Peters, 1968). A possible explanation for survival advantage could be that the effect of pregnancy is like the beneficial effect of additive hormonal therapy in receptor-positive breast cancer patients (Wile and DiSaia, 1989). Ribeiro *et al.* (1986) also found that women who had subsequent pregnancies did better, though this was not statistically significant. Other studies suggest that pregnancy following breast carcinoma does not influence prognosis, though most describe small numbers of patients (Nugent and O'Connell, 1985; Mignot *et al.*, 1986; Cooper and Butterfield, 1970) and there are no controls for factors such as self-selection of patients who have a good prognosis. However, some studies have assessed effects in patients with positive as well as negative nodes at diagnosis and found no detrimental influence of subsequent pregnancy on prognosis (Ribeiro *et al.*, 1986; Ariel and Kempner, 1989; Cooper and Butterfield, 1970). Ariel and Kempner (1989) note a 10-year survival rate for patients with positive lymph nodes who became pregnant after undergoing a mastectomy, which was almost the same as that for patients who had axillary node metastases and did not become pregnant. Certainly, there appear to be no data to state that subsequent pregnancies, in the absence of recurrent disease, are detrimental in this group of women.

Women with previous breast cancer are often advised to delay any subsequent pregnancy until the possibility of early recurrence is over. Clark and Reid (1978) have shown that the interval from treatment to first pregnancy is significantly related to survival. Patients who became pregnant within 6 months of treatment had a poor prognosis, with a survival of 54% at 5 years compared with 100% at 5 years for those who became pregnant 2–5 years after treatment. Delay is usually recommended since recurrence rates are highest in the first 2 years after mastectomy, then gradually fall (Donegan, 1972). In the present study, the time interval between breast cancer diagnosis and beginning of a subsequent pregnancy ranged from 5 months to 7 years 5 months. There was no evidence that outcome for these patients was influenced by the length of this time interval.

In our study, no significant alteration in overall survival was demonstrated for women deciding to undertake a subsequent pregnancy compared to non-pregnant women. However, it was not possible to adequately control for other confounding factors which may have been associated with a decision to undertake a later pregnancy. Nevertheless, there is no evidence to suggest that avoidance of pregnancy after breast cancer diagnosis alters prognosis.

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APPENDIX

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