Eur J Cancer, Vol. 28A, No. 6/7, pp. 1148–1153, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Pregnancy-related Factors and Risk of Breast Cancer in a Prospective Study of 29 981 Norwegian Women

Lars J. Vatten and Stener Kvinnsland

It has been suggested that pregnancy is associated with a short-term increased risk of breast cancer followed by a life-long protection. We studied 340 incident cases of breast cancer in relation to parity, age at first full term birth, and time since last child birth during 14 years follow-up in a prospective cohort of 29 981 Norwegian women. We found no evidence for a transient increase in risk of breast cancer subsequent to pregnancy followed by a reduction in risk of long lasting duration. However, our results indicate that up to an approximate age of 45 years, the nulliparous have a lower breast cancer risk than everparous women. Among parous women, there was an increasingly protective effect on breast cancer risk at a young age (<50 years) with increasing number of child births, independent of age at first birth, whereas the protection associated with an early age at first full term pregnancy may increase in importance with increasing age. This finding may reconcile conflicting reports related to these two factors. This study confirms the results of previous investigations suggesting that a "cross-over" in breast cancer incidence between nulliparous and ever-parous women appears to take place some time during the fifth decade of life.
Eur J Cancer, Vol. 28A, No. 6/7, pp. 1148–1153, 1992.

INTRODUCTION

ALTHOUGH PAROUS women have a reduced lifetime risk of breast cancer compared with nulliparous, evidence suggests that parous women are at increased risk during their reproductive period compared with nulliparous women [1–6]. What has been termed a "cross-over" in risk [2] may appear some time during the fifth decade of life [3], after which parous women experience a lower risk of breast cancer than nulliparous. This effect may be reflected in a study which showed that before the age of 40 breast cancer mortality was higher in married than in single women [1]. Recently prospectively collected data from the Nurses' Health Study could demonstrate that before the age of 50 nulliparous women have a lower risk of breast cancer than everparous women [3]. Moreover, two case-control studies have suggested that a full term pregnancy is immediately followed by a transient increase in the risk of breast cancer over and above the increase associated with ageing alone [7, 8]. Despite the convincing evidence for a long term protection, this may suggest that pregnancy is associated with a short term increase in the risk of breast cancer.

These results have received only moderate attention in the literature, and further exploration of pregnancy-related factors and breast cancer risk in women during reproductive age seems warranted. In particular, the cross-over in breast cancer risk between nulliparous and everparous women need further evaluation, and the association with time since last birth should be verified, specifically addressing the magnitude and duration of a possible increased risk associated with pregnancy.

In this study of nearly 30 000 Norwegian women, prospectively followed-up for approximately 14 years, we therefore make an attempt to approach these questions.

Correspondence to L.J. Vatten.
L.J. Vatten and S. Kvinnsland are at the Department of Oncology, University Hospital, N-7006 Trondheim; L.J. Vatten is also at The Norwegian Cancer Registry, Montebello, N-0310 Oslo 3, Norway.
Revised 13 Feb. 1991; accepted 24 Dec. 1991.

SUBJECTS AND METHODS

Study population

Between 1974 and 1978 all men and women between 35 and 49 years of age and samples of women aged 20 to 34 who were living in three separate counties in Norway were invited to participate in a health screening examination. A second screening took place in the same counties between 1978 and 1983. All residents who were invited to the first screening were also invited to the second. Additional invitations were sent to all residents aged 35–49 at the second screening, and to samples 20–34 years of age. The two screenings were carried out in identical ways, and included a questionnaire, measurements of blood pressure, height and weight, and a non-fasting blood sample was obtained from each subject. The procedures and results of the first and second screening have been described in detail [9–11].

In all, 36 286 women born between 1925 and 1960 attended one of the two screenings. These include between 94 and 97% of all women aged 35–49 years at invitation in the three counties, whereas attendance in samples who were 20–34 years was approximately 84 to 87% [11]. Computer linkage to the Cancer Registry made it possible to ascertain that 340 incident cases of breast cancer were diagnosed in the population during a mean follow-up of 13.8 years (range: 7–16 years). These cases had all developed in women born between 1925 and 1948. Since the objective of this study was to analyse the relation between age- or time-related events and risk of breast cancer, we decided to restrict the analyses to women who were born within this time interval. Furthermore, we excluded all women who had been diagnosed with a cancer (including breast cancer) prior to the year of health screening. Thus, we could include 26 626 women who attended the first, and 3 355 who only attended the second screening, to give a total of 29 981 women eligible for analysis.

Study factors

Based on the official person number of every citizen the Central Bureau of Statistics of Norway has constructed a data file which links a woman to her children [12]. Information provided from this file made it possible to define and further categorise factors related to each woman's reproductive history. The absolute age at first term birth and age at last term birth were both divided into 5-year categories (≤24, 25–29, 30–34, ≥35). Parity was partly studied as the number of births (0, 1, 2, 3, 4, or ≥5), and partly dichotomised into relatively low (1–3 children) or high (≥4 children) parity. To evaluate the risk of breast cancer related to time since last term pregnancy, we adopted a nested case-control approach [13] to reduce potential problems related to the time-age element of the analysis. For each case of breast cancer we randomly selected 10 women as controls among individuals born in the same year as the case. Then we computed time since last birth as the interval between year at diagnosis and year of last birth for both the case and her respective controls. This interval was arbitrarily categorised into four separate groups (0–5, 6–10, 11–15, and >15 years since last birth). Breast cancer risk in women who had their last birth more than 15 years earlier was chosen as a reference.

Statistical analyses

In the analyses we adopted two separate strategies. With the exception of time since last birth, observation years at risk of developing breast cancer were calculated for categories of each reproductive variable during follow-up. A woman was withdrawn from risk at the time of diagnosis of breast cancer, at death from a cause other than breast cancer (information provided by the Central Bureau of Statistics), or at the end of follow-up, whichever event occurred first. This enabled computation of person-time based incidence rates of breast cancer for each of the study variables [13].

Relative risks [termed incidence rate ratio (IRR)] were computed as the rate in a specific category of a study variable divided by the estimated rate of the defined reference category for that variable. The estimated IRRs were adjusted for 5-year categories of age at screening, applying Mantel–Haenszel estimation procedure in a stratified analysis [13], and Mantel's extension test was used for the testing of trends over categories of each variable [14]. The precision of the estimated IRRs was assessed by 95% confidence intervals, using Miettinen's test-based method, applying Mantel–Haenszel χ^2 statistics [14].

Secondly, to analyse the relation between a study factor and the risk of breast cancer, and simultaneously adjust for other reproductive factors with a potentially confounding effect, we fitted the data to multiple logistic regression models, using maximum likelihood statistics [14]. Instead of using person-time based incidence rates this technique computes risk odds of breast cancer, and was applied in age-specific analyses of parity and age at first term birth. Breast cancer risk was separately studied for the following intervals of age at diagnosis: ≤44, 45–49, 50–54, and ≥55. In the analysis of each age-specific stratum women were included who had been at risk of developing breast cancer within this particular age interval at some time during follow-up.

Estimation of multivariately adjusted relative risks [termed risk ratios (RR)] were based on the parameter value of each specific exposure factor according to the methods described by Kleinbaum *et al.* [14].

In the case-control approach of the variable time since last birth, analogous analyses were performed, respectively using Mantel–Haenszel estimation procedures and multiple logistic regression [14].

Table 1. Incidence rate ratio (IRR) and risk ratio (RR) of breast cancer, according to number of full term child births

	Cases	Persons	Person years	IRR*	95% CI	RR‡	95% CI
1	44	3476	47090	1.0†		1.0†	
2	105	8473	115466	1.01	(0.71, 1.43)	1.00	(0.82, 1.21)
3	91	7673	106184	0.93	(0.65, 1.34)	0.95	(0.78, 1.17)
4	34	4262	60300	0.64	(0.41, 0.99)	0.80	(0.63, 1.03)
≥5	20	3064	44008	0.51	(0.30, 0.85)	0.73	(0.54, 0.98)
Nulli-parous	46	2920	39029	1.27	(0.84, 1.92)		

*Adjusted for age (5-year categories), using Mantel–Haenszel estimates. χ^2 test for trend (excluding nulliparous women) = 11.28, $P = 0.001$.
†Reference category.
‡Adjusted for age (5-year categories) and age at first birth, using multiple logistic regression estimates.

RESULTS

The overall results in Table 1 suggest that having four or more children has a protective effect on the risk of developing breast cancer, over and beyond the protection provided by an early first term birth. After adjustment for age and age at first birth, there was a relative risk of 0.73 (95% CI, 0.54, 0.98) in women who had five or more children, compared with women with only one child. The decrease in risk with increasing number of full term births was statistically significant ($\chi^2 = 11.28$, $P = 0.001$), although the effect could mainly be attributed to women with many children. Thus, comparing the pooled risk in women of high parity (≥4 children) with the risk in women of lower parity (1–3 children), the age-adjusted incidence rate ratio was 0.58 (95% CI, 0.43, 0.78).

Analogously, comparing the risk in nulliparous with the pooled risk of everparous women shows that overall, nulliparous women have a 50% increased risk of breast cancer in these data (age-adjusted IRR = 1.50, 95% CI, 1.10, 2.04).

The age-specific analyses in Table 2 suggest that the association between parity and breast cancer risk may vary with age. Nulliparous women have a lower risk than women of parity 1–3 before age 45, after which their rates seem to cross some time between the age of 45 and 49 (Fig. 1). Figure 1 further suggests that after the cross-over the increase in breast cancer risk is apparently stronger in nulliparous that it is in everparous women. Women of high parity (≥4 children) appear to have a life-long protection against breast cancer starting already early in life, and do not seem to experience any period of increased risk. With increasing age, however, the risks in women of high and low (1–3 children) parity seem to converge, especially in women 50 years and older.

The age-adjusted estimates in Table 3 confirm that overall, there is a positive association between age at first full term birth and risk of breast cancer. It also shows that women who have their first term birth at age 35 or older, have a higher risk than nulliparous women. After adjustment for parity, however, the increase in risk with increasing age at first birth does not show a statistically significant association. The age-specific analyses in Table 4 may suggest that the protective influence of an early first birth is more important later in life than it is before the age of 50. Taken together, Tables 2 and 4 may indicate that the

Table 2. Risk ratio (RR) of breast cancer, according to number of full term child births, by categories of age at diagnosis

	Age at diagnosis							
	≤44 (69 cases)		45–49 (109 cases)		50–54 (80 cases)		≥55 (82 cases)	
	RR*	95% CI	RR*	95% CI	RR*	95% CI	RR*	95% CI
1–3 children	1.0†		1.0†		1.0†		1.0†	
≥4 children	0.5	(0.4, 0.8)	0.7	(0.6, 1.0)	0.9	(0.7, 1.2)	0.9	(0.7, 1.2)
Nulliparous	0.9	(0.6, 1.4)	1.1	(0.8, 1.4)	1.2	(0.9, 1.6)	1.2	(0.9, 1.6)

*Adjusted for age (5-year categories) and age at first birth, using multiple logistic regression estimates.
†Reference category.

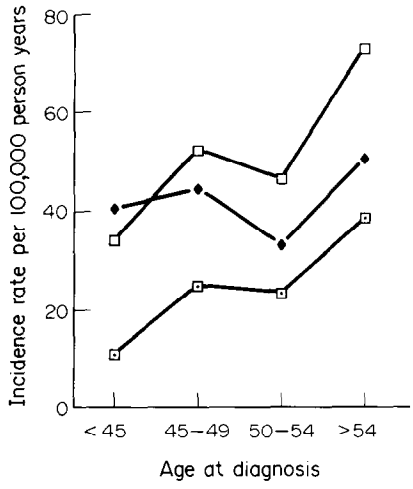

Fig. 1. Incidence rate of breast cancer, by parity and age at diagnosis. —⊡— >3 children, —◆— 1–3 children, —□— nulliparous.

protective effects of parity and age at first term birth may be exerted at different periods in a woman's life. The results suggest that high parity (≥4 children) may be particularly important before age 50, independent of age at first term birth. After this age, however, the protective importance of an early first birth becomes evident, and births subsequent to the first may not provide any substantial additional protection.

We also analysed the relation between age at last birth and risk of breast cancer. The results in Table 5 show no overall association, and the age-specific analyses (data not shown) also failed to detect any effect related to this variable.

Table 6 shows the relation between time since last birth and risk of breast cancer. We did not find any evidence linking a particular risk in breast cancer to the time period subsequent to a woman's last birth.

DISCUSSION

This prospective study of 29981 women provides some evidence that what has been termed a "cross-over" [2] in breast cancer risk between nulliparous and everparous women takes place some time during the fifth decade of life. In accordance with this, the results indicate that the risk of women who had their first pregnancy after the age of 35 is persistently increased compared with that of nulliparous women. At large these results confirm findings of several previous investigations [1–4, 20]. On the other hand, we could not find any clear association between the time interval since last term pregnancy and breast cancer risk. Thus, we were unable to verify the results of studies [7, 8] claiming that following a last term birth, there is a transient increase in breast cancer risk followed by a life-long protection.

The design of this study has several reassuring features for the validity of its results. The prospective design, including a very large proportion of all eligible women in a general population, and a reliable ascertainment of incident cases of breast cancer [15] over approximately 14 years of follow-up, are all factors that strengthen this study. Nevertheless, information on age at first term birth may be subject to some misclassification in women born between 1925 and 1935 (55.4% of the cohort), since a mother could be less reliably linked to a child born before 1953 than after this year [12]. However, the potential bias

Table 3. Incidence rate ratio (IRR) and risk ratio (RR) of breast cancer, according to age at first full term pregnancy

	Cases	Persons	Person years	IRR*	95% CI	RR‡	95% CI
<25	141	15350	212933	1.0†		1.0†	
25–29	111	8270	114154	1.39	(1.08, 1.79)	1.17	(1.02, 1.34)
30–34	26	2458	33706	1.09	(0.72, 1.66)	0.96	(0.76, 1.22)
≥35	16	900	12255	1.77	(1.04, 3.00)	1.20	(0.86, 1.67)
Nulliparous	46	2920	39029	1.65	(1.18, 2.31)		

*Age-adjusted (5-year categories), using Mantel–Haenszel estimates. χ^2 test for trend (excluding nulliparous women) = 5.42, $P = 0.02$.
†Reference category.
‡Adjusted for age (5-year categories), and parity, using multiple logistic regression estimates.

Table 4. Risk ratio (RR) of breast cancer, according to age at first full term birth, by categories of age at diagnosis

	Age at diagnosis							
	≤44 (69 cases)		45–49 (109 cases)		50–54 (80 cases)		≥55 (82 cases)	
	RR*	95% CI	RR*	95% CI	RR*	95% CI	RR*	95% CI
≤24	1.0†		1.0†		1.0†		1.0†	
25–29	1.2	(0.9, 1.6)	0.9	(0.7, 1.1)	1.2	(0.9, 1.6)	1.5	(1.1, 1.9)
30–34	1.1	(0.7, 1.7)	1.0	(0.8, 1.4)	0.9	(0.6, 1.6)	0.9	(0.5, 1.5)
≥35	—		1.0	(0.6, 1.7)	1.6	(1.0, 2.5)	1.7	(1.1, 2.7)
Nulliparous	1.1	(0.7, 1.7)	1.1	(0.3, 5.1)	1.4	(1.0, 1.9)	1.5	(1.1, 2.1)

*Adjusted for age (5-year categories) and parity, using multiple logistic regression estimates.
†Reference category.

Table 5. Incidence rate ratio (IRR) and risk ratio (RR), according to age at last full term birth

	Cases	Persons	Person years	IRR*	95% CI	RR‡	95% CI
<25	38	2965	40341	1.0†		1.0‡	
25–29	67	7714	105851	0.65	(0.43, 0.97)	0.87	(0.69, 1.09)
30–34	100	8899	123087	0.83	(0.57, 1.21)	0.95	(0.76, 1.19)
≥35	89	7400	103769	0.85	(0.57, 1.27)	1.05	(0.73, 1.22)
Nulliparous	46	2920	39029	1.21	(0.77, 1.89)		

*Adjusted for age (5-categories), using Mantel–Haenszel estimates.
†Reference category.
‡Adjusted for age (5-year categories), and parity, using multiple logistic regression estimates.

resulting from this is likely to be non-differential and cause the effects of age at first term birth on breast cancer risk to be conservatively estimated [13].

The presence of a transient breast cancer increase would typically have appeared in relatively young women, and might have been a reasonable explanation for the "cross-over" effect [2], where premenopausal everparous women seem to have a higher risk of breast cancer than nulliparous women [3]. Despite our failure to detect any such association, we spent considerable effort controlling the various elements of time (age, calendar year, time since pregnancy) in the analysis. In the case-control approach very close matching on age between cases and controls was crucial for the estimates of the relative risk. By allowing only small differences in age we observed considerable fluctuations in the odds ratio, suggesting that insufficient control with age may be a particular problem in this type of study. Since the association between "time since an event" and a particular outcome is not a rare study question, this may suggest that a general methodological scrutiny is warranted.

Table 6. Relative risk (RR) of breast cancer, according to the number of years since last birth

	Cases	Controls	RR (M-H)*	95% CI	RR (LR)‡	95% CI
>15 years	183	1963	1.0†			
11–15	57	611	1.0	(0.7, 1.4)	1.0†	
6–10	44	340	1.5	(1.0, 2.2)	1.0	(0.8, 1.2)
0–5	10	135	0.9	(0.4, 2.0)	1.2	(0.9, 1.5)
Nulliparous	46	351	1.3	(0.9, 1.9)	0.9	(0.6, 1.3)

*Mantel–Haenszel estimation procedure.
†Reference category.
‡Adjusted for parity, and age at first birth, using multiple logistic regression estimates.

Nonetheless, the repeated finding that a late first pregnancy gives a persisting increase in breast cancer risk, also compared with nulliparous women, suggests that pregnancy does not always provide protection. Indeed, at a young age, say, before 45, there seems to be a generally higher rate of breast cancer in parous than in nulliparous women. In a certain proportion of women, with preclinical lesions in the breast, growth promoting properties of pregnancy may advance the development of clinical tumours and cause earlier presentation [16]. At a young age, the risk increasing effect of pregnancy is superimposed on a very low background risk, and a predominant effect of pregnancy may be to cause differentiation of breast tissue [17, 18], which, unless initial carcinogenic events have occurred, will result in a life long protective effect. At a later age (say, after 35) the risk increasing effect will, and perhaps more so if not preceeded by previous births, be superimposed on a background risk which is increasing exponentially with age [19]. At this age the risk increasing effect is likely to be of greater importance, and cause more cases to present earlier. Consequently, following a late pregnancy it may take a longer time for the beneficial effects to outweigh the risk increasing effects. As confirmed in this study, a woman whose first term pregnancy happens after age 35, may not experience any beneficial effect on her risk of developing breast cancer [20].

For parous women with other reproductive histories the risk pattern is more complicated. The results of the Nurses' Health Study [3] suggested that women of high parity (≥4 children) are at increased risk until about age 40 compared with nulliparous

women, and that women of lower parity (1–3 children) may not "cross-over" until the second half of the fifth decade of life.

Our results confirm that women of relatively low parity are at increased risk until some time between 45 and 49 years of age. For women of high parity we found an overall strong protection, but were unable to study their risk at a young age, since before age 45, only 6 cases of breast cancer had occurred in women who had ≥4 children in this cohort. However, for women who had a late first birth (≥35 years) our results confirm the overall increased breast cancer risk compared with that of nulliparous women.

These observations indicate that not only the timing of childbearing is important, but also the number of full term pregnancies may determine the appearance of the pregnancy-related risk curve of breast cancer. On the whole, women who have ≥4 children may consequently experience a risk increase of a shorter duration than women of lower parity. This may be particularly true if births take place before the age of 30.

A full term pregnancy constitutes an extended period of potent oestrogen and progesterone stimulation on breast tissue. If early carcinogenetic events have taken place in breast tissue, hormone stimulation may, broadly speaking, serve two functions. It may on the one hand act as a strong growth factor, and have a promoting effect on the tumour [21, 22]. On the other hand, it may serve the function of a pharmacological agent, causing involution of the lesion, and thus, be a strong antipromotor [16]. The results of this study suggest that the latter function will be of greater benefit to women of high parity, and the growth enhancing effect of pregnancy will predominate in women who had their first term birth at an age older than 35.

It has been suggested that the perimenopausal state is accompanied by an increased incidence of breast cancer [23], and advancing menopause to a younger age may be the single most effective way to reduce breast cancer rates [24]. Whereas potent oestrogen influence repeated through several pregnancies may benefit breast tissue through its intensive pharmacological stimulation, introduction of menopause may be equally beneficial, but through an opposite, oestrogen-deprivation mechanism [19]. The net effect of both these mechanisms may be regression of a preclinical lesion, an extended latent phase of disease, or even prevention of its initiation.

After menopause the distinction between incidence in women of high and low parity may no longer be productive. Whereas women of high parity appear to be protected throughout life, their incidence rate may converge with age towards that of women of lower parity. To achieve the long term protective effect associated with pregnancy, this may imply that having had an early first term birth may be the important factor. Possibly, differentiation of breast tissue which occurs throughout first pregnancy may be the overall protective mechanism in everparous women [18, 20]. After menopause, there appears to be a simultaneous divergence in the incidence rates of everparous and nulliparous women (Fig. 1), which may confirm the lack of any protection associated with child births in nulliparous women.

These observations may reconcile previous conflicting reports addressing parity and age at first term birth [5, 20, 25–27], since we found these two variables to have different effects on breast cancer rates at different ages. The importance of parity may be restricted to the age before 50, since during this period being of high parity was inversely related to breast cancer risk, independent of age at first term birth. After this age, the converging breast cancer rates between women of high (≥4 children) and lower (1–3 children) parity suggest that in the long term, protection may be associated with an early age at first term birth, and that births subsequent to the first may not provide any additional long term protective effect.

This study suggests that the relation between pregnancy and breast cancer risk depends on a woman's age. Whereas pregnancy provides an overall protection against breast cancer, nulliparous women have a lower risk than everparous until a "cross-over" takes place at approximately 45 years of age, after which the risk of breast cancer is higher in nulliparous than in everparous women.

1. Logan WP. Marriage and childbearing in relation to cancer of the breast and uterus. *Lancet* 1953, **II**, 1199–1202.
2. Janerich DT, Hoff MB. Evidence for a crossover in breast cancer risk factors. *Am J Epidemiol* 1982, **116**, 737–742.
3. Pathak DR, Speizer FE, Willett WC, Rosner B, Lipnick RJ. Parity and breast cancer risk: possible effect on age at diagnosis. *Int J Cancer* 1986, **37**, 21–25.
4. Lubin JH, Burns PE, Blot WJ, *et al.* Risk factors for breast cancer in women in northern Alberta, Canada, as related to age at diagnosis. *J Natl Cancer Inst* 1982, **68**, 211–217.
5. Kvåle G, Heuch J, Eide GE. A prospective study of reproductive factors and breast cancer. I. Parity. *Am J Epidemiol* 1987, **126**, 831–841.
6. Negri E, La Vecchia C, Bruzzi P, *et al.* Risk factors for breast cancer: pooled results from three Italian case-control studies. *Am J Epidemiol* 1988, **128**, 1207–1215.
7. Bruzzi P, Negri E, La Vecchia C, *et al.* Short term increase in risk of breast cancer after full term pregnancy. *Br Med J* 1988, **297**, 1096–1098.
8. Williams EMI, Jones L, Vessey MIP, McPherson K. Short term increase in risk of breast cancer associated with full term pregnancy. *Br Med J* 1990, **300**, 578–579.
9. Bjartveit K, Foss OP, Gjervig T, Lund-Larsen PG. The cardiovascular disease study in Norwegian counties. Background and organization. *Acta Med Scand* 1979, Suppl no 634.
10. Bjartveit K, Foss OP, Gjervig T. The cardiovascular disease study in Norwegian counties. Results from first screening. *Acta Med Scand* 1983, Suppl no 675.
11. The Cardiovascular Disease Study in Norwegian Counties. Results from Second Screening. The National Health Screening Service, Oslo 1988.
12. Brunborg H, Kravdal Ø. Fertility by birth order in Norway. Report 86/27, Central Bureau of Statistics of Norway, Oslo 1986.
13. Rothman KJ. *Modern Epidemiology*. Boston, Little, Brown and Company, 1986.
14. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Research: Principles and Quantitative Methods*. New York, Van Nostrand Reinhold Company, 1982.
15. Lund E. Pilot study for the evaluation of completeness of reporting to the Cancer Registry. In: *Incidence of Cancer in Norway* 1978. The Cancer Registry, Oslo 1981, 11–15.
16. Henderson IC, Canelos GP. Cancer of the breast. The past decade. *N Engl J Med* 1980, **302**, 17–30, 78–90.
17. Anderson TJ, Ferguson DJP, Raab G. Cell turnover in the "resting" human breast: influence of parity, contraceptive pill, age and laterality. *Br J Cancer* 1982, **46**, 376–382.
18. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. *Breast Cancer Res Treat* 1982, 2, 5–73.
19. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. "Hormonal" risk factors, "breast tissue age" and the age-incidence of breast cancer. *Nature* 1983, **303**, 767–770.
20. MacMahon B, Cole P, Lin TM, *et al.* Age at first birth and breast cancer risk. *Bull WHO* 1970, **43**, 209–221.
21. Lippman ME, Bolan G, Huff K. The effects of estrogens and antiestrogens on hormone-responsive human breast cancer in long-term tissue culture. *Cancer Res* 1976, **36**, 4595–4601.
22. Howell A. Clinical evidence for the involvement of estrogen in the development and progression of breast cancer. *Proc Royal Soc Edinburgh* 1989, **95B**, 49–57.

23. Alexander FA, Roberts MM. The menopause and breast cancer. *J Epidemiol Comm Hlth* 1987, **41**, 94–100.
24. Pike MC. Hormonal contraception with LHRH agonists and the prevention of breast and ovarian cancer. In: Mann RD, ed. *Oral Contraceptives and Breast Cancer* Carnforth, Parthenon Publishing Group. 1990, 323–348.
25. Kelsey JL. A review of the epidemiology of breast cancer. *Epidemiol Rev* 1979, **1**, 74–109.
26. Kvåle G, Heuch I. A prospective study of reproductive factors and breast cancer. II. Age at first and last birth. *Am J Epidemiol* 1987, **126**, 842–850.
27. Lund E. Childbearing in marriage and mortality from breast cancer in Norway. *Int J Epidemiol* 1990, **19**, 527–531.

Acknowledgements—This research is based on data made available by the Cancer Registry, the National Health Screening Service, and the Central Bureau of Statistics of Norway. Dr Vatten is a research fellow of the Norwegian Cancer Society.

Eur J Cancer, Vol. 28A, No. 6/7, pp. 1153–1161, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Host Factors and Breast Cancer Growth Characteristics

David M. Ingram, Anthony Roberts and Elizabeth M. Nottage

The rate of growth and spread of breast cancer varies considerably from patient to patient. An observational study was undertaken to identify possible associations between breast cancer growth characteristics and a wide variety of host factors, including demographic, anthropometric, hormonal and dietary variables in 91 patients with breast cancer. Increasing age was associated with favourable growth characteristics, while previous tonsillectomy was associated with adverse growth characteristics. There were no significant associations in anthropometric variables. For postmenopausal women, increasing bioavailability of oestradiol was associated with favourable growth characteristics, while increasing prolactin concentration was associated with adverse growth characteristics. Increasing consumption of sugar, fibre, fruit and vegetables and vitamins was associated with favourable growth characteristics. Consumption of fat (monounsaturated and saturated) was associated with adverse characteristics when adjustment was made for total energy intake. The host environment may play a role in the control of breast cancer growth. In particular, the associations with oestrogen and progesterone receptor status indicate that nutrients may be of value as biological response modifiers in patients having hormonal therapy. This requires further investigation to assess therapeutic potential.
Eur J Cancer, Vol. 28A, No. 6/7, pp. 1153–1161, 1992.

INTRODUCTION

THE RATE of growth and spread of breast cancer varies considerably from patient to patient. Some patients with apparently early disease at diagnosis die rapidly from widespread metastases, while other patients may report a breast lump which has barely changed over several years, yet biopsy confirms it to be malignant.

The growth of breast cancer is determined in part by the genetic make-up of the cell, and in part by a variety of host factors which may influence the local milieu around the breast cancer cells. The best-known of these host factors is the oestrogen environment, alteration of which by oophorectomy or by oestrogen receptor competitors may halt tumour growth or result in regression of the tumour [1].

To explore the possibility that some of the many host variables, as well as the oestrogen environment, may influence breast cancer growth, an observational study was undertaken to identify possible associations between breast cancer growth characteristics and a wide variety of host factors. If host factors which influence breast cancer growth can be identified, modification of these variables may open new avenues by which tumour growth can be influenced. Variables studied included demographic, anthropometric, hormonal and dietary variables in 91 patients with breast cancer.

Correspondence to D. M. Ingram.
D. M. Ingram and E. M. Nottage are at the University Department of Surgery, Queen Elizabeth II Medical Centre, Perth, Western Australia 6009; A. Roberts is at Ballarat Base Hospital, Victoria, Australia.
Revised 23 Sept. 1991; accepted 21 Nov. 1991.

METHODS

Patients

91 women were identified as having early breast cancer from the pathology records at the Queen Elizabeth II Medical Centre, Perth, Western Australia. Each of these women had undergone surgery for early breast cancer and had consented to take part in the study. At around 3 months after the operation for their primary lesion, the women were interviewed at home using a structured questionnaire, had a morning, mid-luteal blood sample taken, each completed a food frequency questionnaire in regard to their dietary habits up to and including the time of the diagnosis of early breast cancer, and each had measurements of height, weight and subscapular skinfold thickness taken.