Parity and breast cancer: evidence of a dual effect

K L WOODS, S R SMITH, J M MORRISON

Summary and conclusions

Epidemiological studies have shown that early first pregnancy reduces the risk of developing breast cancer, which indicates that initiation of the disease occurs at an early age. Thus the subclinical lesion of breast cancer might already be present in the breast before childbearing begins and the growth of any such focus might be modified by the endocrine changes of pregnancy. To test this hypothesis the relation between parity and age at presentation was studied in 341 unselected patients with breast cancer presenting to a single clinic. The mean age at presentation was 5·2 years lower in parous than nulliparous women ($p < 0.001$) and fell with increasing parity.

It is concluded that reproductive history influences not only the risk of breast cancer but also the latent interval of a proportion of breast carcinomas.

Introduction

The risk of developing breast cancer is directly proportional to age at first birth up to the age of 30.[1] This protective effect is confined to the first pregnancy and appears to be lifelong. Speculation that breast cancer may be initiated during the early years of reproductive life[2] is supported by evidence that the breast is most susceptible to radiation-induced carcinogenesis in early adult life.[3] It follows that the latent interval between tumour initiation and clinical presentation may often extend over several decades, during which time tumour growth would be subject to modification by major endocrine events such as pregnancy. Although latency cannot be measured direct, any factor causing appreciable acceleration of tumour growth during the preclinical period would be associated with earlier mean age at presentation. We carried out a study in which age at presentation was examined in relation to parity in a representative series of women with breast cancer.

Methods

Women attending the breast clinic of a single surgeon (JMM) during the period January 1975 to December 1979 were analysed retrospectively. The clinic serves a socially mixed population in the south-western sector of Birmingham. At her first attendance a standard form is completed for each woman, including a detailed gynaecological and obstetric history; this information is recorded before clinical examination or investigation.

From histopathological records 371 women were identified in whom carcinoma of the breast had been finally diagnosed. All malignant lesions of the mammary epithelium were included. On retrieval of the clinical forms 30 (8·1%) of these women had to be excluded from the analysis because of incomplete documentation. The remaining 341 women were not evenly distributed over the quinquennium owing to an increase in referrals during the study period: 50 cases were recruited to the study in 1975 and 150 in 1979.

When reviewing reproductive history we disregarded pregnancies of under 28 weeks' duration. This limit was chosen arbitrarily since endocrine stimulation of the breast increases progressively from about the tenth week to term; however, the response of the breast to the changing hormonal environment is greatest in the last trimester.[4] Abortions were documented for fewer than 4% of subjects in each parity group. This is almost certainly an underestimate of their true incidence, and we were unable to analyse their influence, if any, on age at presentation with breast cancer.

Parametric methods of analysis were used in view of the near-Gaussian distribution of age (fig 1). The small difference in variance of age at presentation in nulliparous and parous women was disregarded in the comparison of means because of the size of the sample. Variances were compared by the variance ratio method for F.

Results

The sample was closely representative of all patients presenting in the West Midlands[5] with respect to mean age, median age, and age distribution (fig 1).

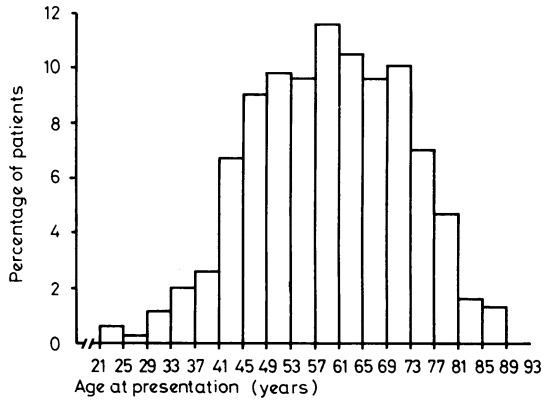

FIG 1—Age distribution at presentation of 341 women with breast cancer.

Figure 2 shows the relation between mean age at presentation and parity. The mean age of all parous women at presentation was highly significantly less than that of nulliparous women ($p < 0.001$), and mean age at presentation fell with increasing parity. The fall in mean age with each of the first two pregnancies was similar and cumulative. There was only a slight further fall in mean age attributable to the third and subsequent pregnancies. The variance of mean age was slightly greater for parous than nulliparous women (table I).

To eliminate undue bias by extremes of age, the women in each parity group were subdivided about the median age for the whole sample (59 years) to produce a contingency table (table II). The excess of younger women in higher-parity groups was significant ($\chi^2 = 8.34$, $p < 0.05$).

The sample showed the expected association between increasing parity and falling mean age at first pregnancy (para 1, 28·9 years; para 2, 26·0 years; para 3 or more, 23·3 years; overall mean, 25·8 years).

The first pregnancies of the women in the sample were distributed over the years 1918-76, when there was an overall upward trend in general fertility rate[6] due largely to low fertility during the 1940s. This demographic change would tend to produce a weak association

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between higher parity and younger age in any randomly selected group of women. Since 1946, however, the general fertility rate has shown no overall upward trend. We therefore repeated the analysis considering only those women aged under 58 years at presentation. Parous women were again significantly younger at presentation than nulliparous women ($p < 0.05$), despite a considerably reduced sample size (151 women).

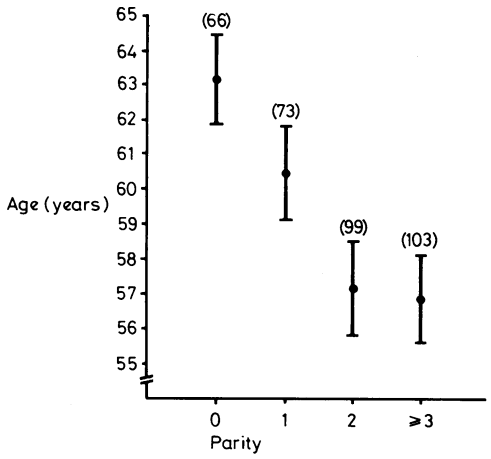

FIG 2—Mean age at presentation (±SEM) according to parity. Sample size given in parentheses.

TABLE I—*Mean age at presentation according to parity*

	No of patients	Mean age at presentation (years)	SD	SE
Nulliparous	66	63·1*	10·6†	1·3
All parous	275	57·9*	12·9†	0·8

*Comparison of means: $p < 0.001$.
†$F = 1.48$; $p = 0.05$ (two-tailed).

TABLE II—*Contingency table showing numbers of women presenting at 58 years and below and 50 years and below according to parity*

Parity	No of patients	No (%) presenting at 58 years and below*	No (%) presenting at 50 years and below
0	66	22 (33)	10 (15)
1	73	32 (44)	14 (19)
2	99	52 (53)	31 (31)
≥3	103	56 (54)	40 (39)

*$\chi^2 (4 \times 2) = 8.34$; $p < 0.05$.

Discussion

The method of recruitment to the study makes it unlikely that our results were due to bias in the sample. Moreover, the age distribution of the sample was essentially the same as that of patients with breast cancer recorded by the Birmingham Cancer Registry. The Registry serves about one-tenth of the population of Britain and registers over 95% of cases in the region.

The 5·2 year age difference between parous and nulliparous women is unlikely to have been due to chance or demographic factors. We believe that it was caused by an effect of pregnancy on the development of some breast carcinomas during their subclinical phase. The greater variance of age at presentation among parous women suggests that only a proportion of carcinomas are accelerated in this way, which is in keeping with the fact that only a few disseminated breast carcinomas show an objective response to endocrine manipulation.[7]

An alternative possibility arises from the studies of MacMahon *et al.*[1] If first pregnancy rendered the breast resistant to tumour initiation then initiation would be largely confined to a narrower time interval in parous than nulliparous women. Assuming a fairly constant latency, mean age at presentation would be lower in parous than nulliparous women. Such a model, however, results in a wider age distribution at presentation among nulliparous than parous women; we found the reverse to be true.

Although the relation between parity and the risk of breast cancer has been studied extensively, an effect of parity on age at presentation has not been reported. Our study provides no information on risk and was not designed to do so. Our conclusion that pregnancy can accelerate tumour growth is entirely compatible with the epidemiological evidence for a protective effect of early first pregnancy provided that a clear distinction is recognised between tumour initiation and development. We propose that pregnancy influences these two processes by separate mechanisms. In support of this, only the first pregnancy appears to modify risk[2]; while our results show that the effect of parity on tumour development is not confined to the first pregnancy.

The mechanism underlying the association between parity and age at presentation is speculative. Any plausible hypothesis requires that the neoplastic lesion is already present at the time of pregnancy. The major endocrine stimuli to the breast in pregnancy include sustained high concentrations of prolactin, oestrogen, and progesterone. Of these, prolonged oestrogen stimulation is most likely to influence tumour-cell kinetics. It would be interesting to know whether tumours of parous women presenting at a young age are more or less likely than others to respond to endocrine treatment.

Although extrapolating observations on animal mammary tumours to the human disease is hazardous, chemically induced tumours of the rat provide an interesting parallel. Prior pregnancy renders the rat mammary gland less susceptible to chemical carcinogenesis,[8] but pregnancy after exposure to the carcinogen shortens the interval between exposure and appearance of tumours.[9 10]

Our findings add further support to the belief that initiation of breast cancer commonly occurs in early adult life. They may also be practically important in the design of screening programmes. The cost-effectiveness, feasibility, and safety of routine breast-cancer screening are being studied in many centres. A working group of the National Cancer Institute recommended[11] that mammographic screening should be confined to women aged 50 years or more in view of the greater risk of radiation carcinogenesis and low detection rate of early cancer in young women. Table II shows that in this study 39% of women of para 3 or more presented at or below 50 years of age. Thus parity should be taken into account when deciding the optimum age at which to begin screening. This point would tend to be obscured in the evaluation of screening programmes, since women of high parity tend to be underrepresented among women with breast cancer by reason of their lower mean age at first pregnancy. By relating age at first screening to parity the effectiveness of the procedure should be improved.

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Conjugal disharmony: a hitherto unrecognised cause of strokes

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Summary and conclusions

Two women of reproductive age suffered strokes. Neither was taking oral contraceptives, and investigations showed no other causal factors. The radiological findings were characteristic of traumatic internal carotid artery occlusion, but neither patient gave a history of trauma. Only after further inquiry into the patients' social circumstances did it emerge that each had survived an attempt at strangulation by her husband.

Such a cause of stroke in young women should be considered when other causes of carotid artery occlusion cannot be identified.

Introduction

Strokes occurring in women of reproductive age are uncommon, and in many cases full investigation fails to detect a demonstrable cause. When such a catastrophe occurs, less common causes of strokes are sought such as blood dyscrasia, bacterial endocarditis, severe diabetes, hypertensive encephalopathy, intracranial tumour, and vascular syphilis. Oral contraceptives, particularly of high oestrogen content, have been aetiologically implicated recently, but the pathogenesis remains unclear. Disease of the extracranial vessels has come to be recognised as a common cause of stroke in older age groups, and this cause for stroke is often seen in younger patients. Bickerstaff,[1] however, found that the lesion was probably in the distribution of the middle cerebral artery, and lesions of the carotid artery in the neck were uncommon. Recognition of the role of non-penetrating trauma in the pathogenesis of internal carotid artery occlusion has increased recently, and the clinical, pathological, and radiological features are now well described.[2-6]

We have recently seen two women of reproductive age who suffered strokes as the result of lesions of the internal carotid artery, which we believe to be a result of a hitherto unrecognised, but probably not uncommon, form of trauma to this vessel in the neck.

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Case reports

CASE 1

Five weeks before admission to this centre, a fit woman aged 37 became mildly confused and complained of headache. Over the succeeding seven days she developed weakness of her right hand, right arm, the right side of her face, and her right leg, followed by sensory diminution in a similar distribution and difficulty with speech. Her left eyelid began to droop, and she was admitted to another hospital then transferred for neurological investigation. Reproductive and menstrual history was unremarkable, and she was not taking oral contraceptives.

On examination she was fully conscious and mildly dysphasic. There was left Horner's syndrome and mild weakness of the right side of her face and of her right arm, with hyperreflexia. Palpation of the carotid arteries in the neck was normal, and there were no bruits. Her heart was in sinus rhythm and her blood pressure 140/90 mm Hg.

Results of the following investigations were normal: haemoglobin concentration; white blood cell count; erythrocyte sedimentation rate; blood film; Wassermann reaction; urea, blood sugar, cholesterol, triglyceride, and electrolyte concentrations; liver function tests; skull and chest radiography; isotope brain scan; and electrocardiography. Left common carotid arteriography showed incomplete occlusion of the internal carotid artery 1·5 cm distal to the bifurcation (fig 1) with sparse flow upwards to fill the ophthalmic artery.

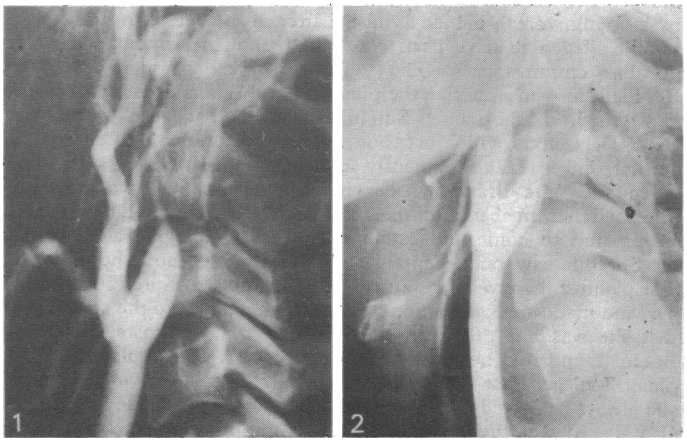

FIG 1—Case 1. Left carotid arteriogram showing almost complete block of internal carotid artery 1·5 cm distal to bifurcation. FIG 2—Case 2. Left carotid arteriogram showing occlusion of internal carotid artery 2 cm distal to bifurcation.