Risk factors relevant to cystic breast disease: a case-control study

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SUMMARY A total of 188 women aged 40–54 with cystic breast disease and 2213 asymptomatic controls were questioned in Edinburgh between 1974 and 1978 concerning marital, reproductive, and menstrual status, history of oral contraception use, history of previous breast complaints, and a family history of breast cancer. Women with a history of breast biopsy were at an increased risk of the disease and those past the menopause were at a decreased risk. These results agree with previous findings that the disease is most prevalent among premenopausal women and suggest that benign cystic disease of the breast does not share a common aetiology with breast cancer in the age range 40–54.

The results from several follow up studies suggest that women with benign cystic disease of the breast are at a twofold risk of developing subsequent breast cancer, compared with normal women^{1–4} (MM Roberts *et al*, submitted for publication). In addition, some case-control studies have indicated that women with breast cancer report a previous biopsy for benign disease more frequently than the controls.^{5–7} These findings have led some workers to believe that the presence of benign changes in the breast are a predisposing factor for cancer, particularly if those changes include atypical proliferation of the epithelium.^{8–9}

One might therefore expect benign disease of the breast to share some aetiological risk factors with breast cancer, though there is disagreement over this issue.^{10–13} Part of the problem may lie in the definition of “benign breast disease.” Some workers refer only to cystic disease (the presence of one or more cysts being readily proved and agreed), others to any lesion in the breast that has been biopsied. Some include women who have symptoms thought to be due to benign disease, but in whom there is no definitive proof: others go so far as to say that the concept of benign breast disease is mistaken, such changes being largely due to physiological reasons.¹⁴

The present study is limited to women who have had proved benign cystic disease compared with age-matched women with normal breasts. Our objective was to determine whether there were predisposing factors for cystic disease and whether they were

related to risk factors known to be of relevance to breast cancer.

Patients and methods

For purposes of continuing research, the medical and sociobiological history of all patients attending the diagnostic clinic in the department of clinical surgery was recorded and entered on to computer from 1974 to 1978. A similar policy existed in the Edinburgh Breast Screening Clinic at about the same time (1975–8). Asymptomatic women attending the screening clinic were invited from the general population, their names having been derived from general practitioner lists.¹⁵ The reasons for the design of this study using cases from the diagnostic clinic and controls from the screening clinic, and the measures taken to adjust for any between clinic bias are given elsewhere.^{7,16} The factors investigated were marital status, menstrual status, reproductive history, breast feeding, use of oral contraceptive pill, previous breast complaint, and family history of breast cancer.

Altogether, there were 188 cases of proved cysts and 2213 controls with no abnormality on screening by clinical and mammographic examination, all aged from 40 to 54. Above the age of 54 there were too few cysts to permit any meaningful analysis. Table 1 shows the age distribution of cases and controls. In almost all cases the presence of a cyst was proved by needle aspiration, in a few by open biopsy.

Any between clinic bias was corrected using a

Table 1 Cystic disease of the breast: age distribution of cases and controls

Age	Cases		Controls	
	No	%	No	%
40-44	77	(41.0)	627	(28.3)
45-49	87	(46.3)	752	(34.0)
50-54	24	(12.7)	834	(37.7)
Total	188	(100.0)	2213	(100.0)

maximum likelihood method on data from 167 women who attended both clinics¹⁶ but who are not included in the present study. The relative risk associated with each factor was calculated, based on the assumption that reporting was correct at the screening clinic for reasons specified elsewhere.⁷ The cyst cases and the controls were directly compared within each age group.

Results

Table 2 shows the reported frequencies of risk factors by cases and controls, together with the relative risk estimates for each age group. Postmenopausal women were at less risk of having cystic disease, which is in keeping with observations that this disease is an essentially premenopausal complaint. Women with a history of breast complaint or biopsy were significantly more likely to have cystic disease. This is not unexpected, as almost all women with cystic disease tend to have recurrent cysts. Reproductive, menstrual factors and a family history of breast

cancer were not significant risk factors in cystic disease. Even when the risks were recalculated including never pregnant women no significant effects were seen (table 3).

Discussion

We have found that the only factors positively associated with benign cystic disease were the menstrual status and a history of breast complaint, particularly if biopsy had been performed. Neither of these is surprising from clinical knowledge of the disease. Interestingly a quarter of the women with cysts had a history of biopsy, which is about four times the rate found in our series of cases of cancer.⁷ It is also greatly in excess of the prevalence of breast biopsy among women.

We found no association with any reproductive factors, in particular previous oral contraceptive use. It is now well accepted that oral contraceptives have a protective effect against benign disease of the

Table 3 Relative risk estimates for reproductive factors including never pregnant women

Risk factor	Relative risk estimate for age groups		
	40-44	45-49	50-54
Five or more live births	1.91	1.37	1.96
History of miscarriage	1.08	0.59	0.95
Ever breast fed	0.90	1.44	3.29
Not pregnant by age 35	1.16	0.57	0.21
Pregnant by age 20	1.89	2.23	3.49

Table 2 Benign cystic disease: reported frequency of risk factors and relative risk estimates (adjusted for between clinic bias)

Risk factor	No (%) of women with risk factor present		Relative risk estimate for age groups		
	Cases	Controls	40-44	45-49	50-54
Married	171 (91)	1773 (80)	1.68	1.48	18.22
Postmenopausal	35 (19)	979 (44)	†	0.31**	0.22***
Ever pregnant	148 (79)	1785 (81)	0.81	1.36	3.68
Five or more live births	12 (6.4)	91 (4.1)	2.14	1.39	1.78
Miscarriage (ever)	38 (20)	499 (23)	1.23	0.52	0.74
Ever breast fed	81 (43)	1053 (48)	0.83	1.32	2.52
Not pregnant by age 35	2 (1.4)	100 (5.7)	0.90	†	†
Pregnant by age 20	13 (9.1)	88 (5.0)	2.14	2.29	3.21
Oral contraceptives (ever)	41 (22)	507 (23)	0.65	0.57	2.67
Previous breast complaint	65 (35)	355 (16)	3.50*	4.88***	9.72***
Previous breast biopsy	45 (24)	76 (3.4)	9.84***	21.37***	38.45***
Family history of breast cancer	21 (11)	293 (13)	0.90	0.81	2.60
Mother with breast cancer	6 (3)	64 (3)	0.73	0.61	5.29
Sister with breast cancer	4 (2)	46 (2)	5.08	0.8	†
Any first degree relative with breast cancer	10 (5)	108 (5)	1.77	0.72	2.27

†No estimate possible.
 *Significant at 1% level.
 **Significant at 0.5% level.
 ***Significant at 0.1% level.

Risk factors relevant to cystic breast disease

breast,^{17 18} though some bias may be engendered by doctors believing its presence is a contraindication to prescribing such drugs.¹⁹ Possibly our lack of association in either direction is because of the low percentage (22%) of women in our groups who had ever been exposed to this factor.

Cysts may simply represent physiological degeneration within the breast. On the other hand, they may reflect an active hormonally controlled process and abnormal serum hormone concentrations have been reported in some women though the evidence is far from convincing.^{20 21} Of perhaps more interest is the finding that some cyst fluids contain large quantities of active steroid conjugates such as DHA sulphate, as well as immunoglobulins and other proteins, suggesting an active metabolic process, though not all cysts are alike.²² Clearly, subgroups may exist, which could be categorised on either biochemical or pathological features, and these may have differing breast cancer risks.

Our study shows no relationship of benign disease to any of the other reproductive factors: it is of clinical interest that pregnancy and breast feeding did not alter the risk of cystic disease. We also found a clear absence of relationship to family history of breast cancer in a close relative. Assuming that our method is reliable, and this question has been discussed elsewhere,^{7 16} we conclude that benign cystic disease of the breast does not share a common aetiology with breast cancer, at least in Scottish women in this age group. This is in agreement with studies in Boston and Finland.^{10 13} Nevertheless, the epidemiological pattern of cystic breast disease is still not well established, and we should not make any assumptions about the existence of risk factors relating to it.

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