

A Case Control Study of Factors Associated with Macroscopic Breast Cysts

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Women who have a breast cyst aspirated are at increased risk of developing breast cancer. We present an age-matched case control study comparing the reproductive characteristics of 352 women who had a breast cyst aspirated with a control group of 352 contemporaneous clinically normal women. Women with breast cysts were more likely to be nulliparous [odds ratio (OR) = 2.28, 95% confidence interval (CI) = 1.34-3.88] or have a late age at first live birth (χ^2 trend = 5.6, $P < 0.025$), and a late menopause (χ^2 trend = 4.3, $P < 0.05$). They were less likely to have ever used the oral contraceptive pill (OR = 0.38, 95% CI = 0.26-0.55) or to have used the pill for a short duration (χ^2 trend = 16.8, $P < 0.001$), and were less likely to have had a hysterectomy (OR = 0.58, 95% CI = 0.36-0.93). They were more likely to wear a small bra (χ^2 trend = 18.6, $P < 0.001$) and bra cup (χ^2 trend = 5.6, $P < 0.025$). Nulliparity, late age at first live birth and late menopause are factors common to breast cancer risk.

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INTRODUCTION

SEVERAL STUDIES have now reported an increased risk of breast cancer in women who have previously had a breast cyst aspirated [1-4]. The reported increased risk varies from 1.7 to 4.4 times that of the general female population [1-4], and is higher in women with multiple cysts [3]. The epidemiology of breast cancer is well documented [5-7], but studies of the epidemiology of benign breast disease have produced divergent findings [8-12]. These reports suffer from the problems of the classification of benign breast disease, and that the index cases are often women with biopsy proven benign disease which introduces further bias. Bundred *et al.* [4] reported a study of 639 women who presented to the Cardiff Breast Clinic, consecutively with a diagnosis of benign nodularity. These women were divided into 352 who had a breast cyst aspirated and 287 who had benign nodularity but no discrete cysts. The breast cancer risk was increased in the women who had breast cysts aspirated compared to the group with benign nodularity alone. Thus it might be expected that the epidemiological factors associated with breast cyst formation would be similar to those of breast cancer.

Our aim was to perform an age-matched case control study to compare the reproductive characteristics of the women who had undergone breast cyst aspiration, in the earlier study [4], with a control group of clinically normal women and to compare the characteristics identified to those known to be associated with breast cancer risk [5-7].

PATIENTS AND METHODS

The 352 cases underwent breast cyst aspiration in the Cardiff Breast Clinic between 1976 and 1982 [4]. They were age-

grouped, using World Health Organization 5-year bands, and the computer database was interrogated to produce 352 age-comparable controls. These controls were referred to the Cardiff Breast Clinic with symptoms within 5 years of the cases, but when seen the clinician found no abnormality, mammography where performed showed no evidence of disease, and the patient was discharged. The notes of the controls were reviewed to check that they had not subsequently developed breast disease. If breast disease had developed they were excluded from the study and a new control matched. The mean ages of cases and controls were 44.9 (S.D. 7.1) years and 44.8 years (7.6), respectively. Data on reproductive characteristics recorded at presentation was recovered from the computer database and compared between the cases and controls. The relative risk of each of the characteristics under study was estimated as odds ratios and trends assessed by the Armitage test for trend [13].

RESULTS

47 (14%) women with breast cysts were nulliparous compared to 22 (7%) controls, nulliparous women had an odds ratio of 2.28 [95% confidence interval (CI) = 1.34-3.88] (Table 1). If they were parous women with breast cysts were likely to have a late age at first live birth (χ^2 trend = 5.6, $P < 0.025$) (Table 2). Fewer women with breast cysts were postmenopausal at presentation, but this difference was not significant (Table 3).

Table 1. Diagnosis and parity

Parity	Cysts	Controls	OR	(95% CI)
Nulliparous	47	22	2.28	(1.34-3.88)
Parous	282	301	1.00	
Missing data	23	29		
Totals	352	352		

OR = odds ratio, 95% CI = 95% confidence interval.

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Table 2. Diagnosis and age at first live birth

Age (years)	Cysts	Controls	OR	(95% CI)
≤19	25	57	0.43	(0.25–0.73)
20–24	142	138	1.00	
25–29	84	76	1.10	(0.75–1.62)
≥30	31	30	1.00	(0.57–1.74)
Total	282	301		

Armitage test for trend, $\chi^2 = 5.6$, $P < 0.025$.

Table 3. Diagnosis and menopausal status

	Cysts	Controls	OR	(95% CI)
Menopausal status				
Premenopausal	286	259	1.00	
Postmenopausal	29	40	0.66	(0.39–1.08)
Hysterectomy	32	52		
Missing data	5	1		
Totals	352	352		

However if they were postmenopausal, the women with breast cysts were likely to have a late menopause (χ^2 trend = 4.3, $P < 0.05$) (Table 4). Women with breast cysts were also less likely to have had a hysterectomy, an odds ratio of 0.58 (95% CI = 0.36–0.93) (Table 5). They were less likely to have ever taken the oral contraceptive pill, 54 (16%) as compared with 114 (32%) controls, women who had ever used the pill had an

Table 4. Diagnosis and age at menopause

Age (years)	Cysts	Controls	OR	(95% CI)
≤44	3	12	0.33	(0.08–1.44)
45–49	12	16	1.00	
≥50	14	12	1.56	(0.53–4.57)
Total	29	40		

Armitage test for trend, $\chi^2 = 4.3$, $P < 0.05$.

Table 5. Diagnosis and hysterectomy

Hysterectomy	Cysts	Controls	OR	(95% CI)
Yes	32	52	0.58	(0.36–0.93)
No	315	299	1.00	
Missing data	5	1		
Total	352	352		

Table 6. Diagnosis and oral contraceptive pill

Pill use	Cysts	Controls	OR	(95% CI)
Never	293	237	1.00	
Ever	54	114	0.38	(0.26–0.55)
Missing data	5	1		
Total	352	352		

Table 7. Diagnosis and duration of oral contraceptive pill use

Duration (years)	Cysts	Controls	OR	(95% CI)
<1	23	18	1.00	
1–2.9	15	27	0.43	(0.18–1.04)
3–9.9	12	48	0.20	(0.08–0.48)
≥10	4	21	0.15	(0.04–0.52)
Total	54	114		

Armitage test for trend, $\chi^2 = 16.8$, $P < 0.001$.

odds ratio of 0.38 (95% CI = 0.26–0.55) (Table 6). The women with breast cysts who had taken the pill had done so for a shorter duration than the controls (χ^2 trend = 16.8, $P < 0.001$) (Table 7). Women with breast cysts were more likely to wear a small bra (χ^2 trend = 18.6, $P < 0.001$), and a small bra cup (χ^2 trend = 5.6, $P < 0.025$) (Table 8). There was no relationship

Table 8. Diagnosis and bra

	Cysts	Controls	OR	(95% CI)
Bra size*				
32–34	117	89	1.50	(1.06–2.13)
36–38	154	176	1.00	
≥40	10	38	0.30	(0.14–0.62)
Not worn	54	25	2.47	(1.47–4.16)
Missing data	17	24		
Totals	352	352		
Bra cup†				
A	67	66	1.02	(0.68–1.54)
B	149	149	1.00	
C	35	64	0.55	(0.34–0.88)
D	7	13	0.54	(0.21–1.39)
Not worn	54	25	2.16	(1.28–3.65)
Missing data	40	35		
Totals	352	352		

* Armitage test for trend, $\chi^2 = 18.6$, $P < 0.001$.

† Armitage test for trend, $\chi^2 = 5.6$, $P < 0.025$.

Table 9. Diagnosis and age at menarche

Age (years)	Cysts	Controls	OR	(95% CI)
≤11	46	73	0.41	(0.24–0.67)
12	54	61	0.57	(0.35–0.93)
13	90	58	1.00	
14	78	63	0.80	(0.50–1.28)
≥15	62	69	0.58	(0.36–0.93)
Missing data	22	28		
Totals	352	352		

Armitage test for trend, $\chi^2 = 3.0$, $P =$ not significant.

with menarche (Table 9). Half as many women with breast cysts were taking the pill at the time of presentation, 11 (3%) as compared to 22 (6%) controls but this was not significant (OR = 0.51, 95% CI = 0.24–1.07).

DISCUSSION

Late age at first live birth and low parity are related and are factors associated with breast cysts in this study, which are also recognised breast cancer risk factors [6]. Whether it is the late occurrence of the hormonal changes which accompany pregnancy or factors, such as anovulatory menstrual cycles, which may delay the first pregnancy that lead to this increased risk of developing breast cysts and breast cancer is not known.

The incidence of clinically presenting benign breast diseases reduces after the menopause. Therefore women who have a late menopause have longer to present with breast cysts, the incidence of which increases in the years before the menopause [14]. Late menopause is a recognised breast cancer risk factor, probably due to increasing the years of menstrual activity [5]. The ovarian status of the women in this study who had undergone a hysterectomy is not known. However, it is likely that the finding women with breast cysts were less likely to have had a hysterectomy is related to an early artificial menopause in some of the controls.

It is generally agreed that the incidence of benign breast disease is reduced in women who take the oral contraceptive pill, particularly in current and long-term users [8, 10, 11, 15–17]. In this study the observation that ever having used the pill was related to a reduced risk of developing breast cysts suggests a long-standing effect, and reduces the likelihood that this finding is due to a reluctance to prescribe the pill to women with breast cysts. The mechanism by which the pill reduces breast cyst formation is not known, but reduction in apocrine secretion may be important [16]. All breast cysts are lined, at least in part, by apocrine epithelium [17] so a reduction of apocrine activity within the breast could explain the reduced breast cyst formation.

Bra cup relates to breast size and body weight [18, 19], and bra size relates to body build. The finding that a small bra cup is associated with breast cysts may simply indicate that a cyst is more easily palpated within a small breast. It is striking that women with breast cysts were much less likely to wear a bra. It could be surmised that women who do not wear a bra have smaller breasts than those who do, but we have no data to support this. Other factors that may be involved are the degree

of breast involution and the weight of the woman. Obese women have previously been shown to have a reduced risk of developing benign breast disease [10, 11], which again may be solely due to difficulty in detecting benign lesions within a large obese breast. In postmenopausal breast cancer, a moderate positive association has consistently been found between body build and cancer risk, but in premenopausal breast cancer a negative association has been found by some [5].

In summary, the reproductive characteristics of the women with breast cysts identified in this study that are common to breast cancer risk factors are late age at first live birth, nulliparity and late menopause. The other positive factors identified, small bra cup and bra size, might be explained by benign lesions being more easily palpated within a small breast. It is interesting that women with breast cysts were less likely to have ever used the oral contraceptive pill or to have used it for a shorter duration. The reason for this remains to be identified, but further study of this effect may be helpful in the development of drug treatments to reduce breast cyst recurrence.

1. Ciatto S, Biggeri A, Del Turco MR, Bartoli D, Iossa A. Risk of breast cancer subsequent to proven gross cystic disease. *Eur J Cancer* 1990, 26, 555–557.
2. Roberts MM, Jones V, Elton RA, Fortt RW, Williams S, Gravelle IH. Risk of breast cancer in women with history of benign disease of the breast. *Br Med J* 1984, 288, 275–278.
3. Haagensen CD. *Disease of the Breast*, 3rd ed. Philadelphia, Saunders, 1986, 259–263.
4. Bundred NJ, West RR, O'Dowd J, Mansel RE, Hughes LE. Is there an increased risk of breast cancer in women who have a breast cyst aspirated? *Br J Surg* 1991, 64, 953–955.
5. Kelsey JL. A review of the epidemiology of human breast cancer. *Epidemiol Rev* 1979, 1, 74–109.
6. Kelsey JL, Berkowitz GS. Breast cancer epidemiology. *Cancer Res* 1988, 48, 5615–5623.
7. Haagensen CD, Bodian C, Haagensen DE. Breast carcinoma risk and detection. Philadelphia, Saunders, 1981, 30–50.
8. Sartwell PE, Arthes FG, Tonascia JA. Epidemiology of benign breast lesions: lack of association with oral contraceptive use. *N Engl J Med* 1973, 288, 551–554.
9. Nomura A, Comstock GW, Tonascia JA. Epidemiologic characteristics of benign breast disease. *Am J Epidemiol* 1977, 105, 505–512.
10. Brinton LA, Vessey MP, Flavel R, Yeates D. Risk factors for benign breast disease. *Am J Epidemiol* 1981, 113, 203–214.
11. Parazzini F, LaVecchia C, Franceschi S, et al. Risk factors for pathologically confirmed benign breast disease. *Am J Epidemiol* 1984, 120, 115–122.
12. Duffy SW, Roberts MM, Elton RA. Risk factors relevant to cystic breast disease: a case-control study. *J Epidemiol Community Health* 1983, 37, 271–273.
13. Armitage P. *Statistical Methods in Medical Research*. Oxford, Blackwell, 1971.
14. Dixon JM. Cystic disease and fibroadenoma of the breast. *Br Med Bull* 1991, 47, 258–271.
15. Ory H, Cole P, MacMahon B, Hoover R. Oral contraceptives and reduced risk of benign breast disease. *N Engl J Med* 1976, 294, 419–422.
16. Royal College of General Practitioners. *Oral Contraceptives and Health*. London, Pitman, 1974, 65–69.
17. Bundred NJ, Miller WR, Walker RA. An immunohistochemical study of the tissue distribution of the breast cyst fluid protein, zinc alpha 2 glycoprotein. *Histopathology* 1987, 11, 603–610.
18. Hsieh C-c, Trichopoulos D. Breast size, handedness and breast cancer risk. *Eur J Cancer* 1991, 27, 131–135.
19. Sasano N, Tateno H, Stemmermann GN. Volume and hyperplastic lesions of the breast of Japanese women in Hawaii and Japan. *Prev Med* 1978, 7, 196–204.