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Original Contributions

EPIDEMIOLOGIC CHARACTERISTICS OF BENIGN BREAST DISEASE[1]

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To see if the risk factors associated with fibroadenoma and cystic disease were similar to those reported for breast cancer, a retrospective study of benign breast tumor in a general population was conducted in Washington County, Maryland. The study population consisted of 320 white women 20 to 49 years of age who had had benign breast disease and 320 age-matched controls. More cystic disease cases than controls had the following characteristics, which had been reported to have been associated with breast cancer in other studies: higher socioeconomic status; fewer pregnancies; and a lack of association with lactation patterns. Nulliparity, late natural menopause and a maternal history of breast cancer were also more common among cystic cases than controls, although these differences could have occurred by chance. Cystic disease cases and controls did not differ with respect to other factors associated with breast cancer, such as early age at menarche, late age at first pregnancy, and negative history of artificial menopause. In contrast to cystic breast disease, fibroadenoma was not associated with most of the risk factors of breast cancer.

breast neoplasms; cancer; cysts; fibroma; mastitis; tumors

If cystic mastitis is pre-cancerous, as suggested by several follow-up studies of women with a previous benign breast lesion (1–4), the etiologic factors for both cystic mastitis and breast cancer should be similar. One way to investigate this possibility is to compare the epidemiologic char-

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acteristics of both conditions. If they share common factors, it would strengthen the argument that cystic disease and cancerous breast lesions are related.

A woman at high risk for breast cancer has the following characteristics: a maternal history of breast cancer (5, 6), early menarche (7-9), fewer offspring or a late first childbirth (10–12), late natural menopause (13, 14), a negative history of artificial menopause (15–17), and high social class status (18).

In contrast to the many epidemiologic studies of breast cancer, there have been only a few of benign breast disease. Five of these studies (19–23) were registry- or hospital-based retrospective investigations. They suggested that benign cases shared only some of the epidemiologic features of breast cancer. As with breast cancer cases, more benign breast cases than controls had a late natural menopause (19, 20) and fewer offspring (19–21). However, benign cases and controls did not differ by age at menarche (19–21). Furthermore, discrepant results were observed in these studies regarding the relationship between benign mammary disease and a family history of breast cancer (20–23), age at first childbirth (19–22), history of artificial menopause (19, 20) and social class status (20, 22). A recent prospective study found that fibrocystic breast disease was inversely related to parity, but unrelated to age at first birth (24).

Because of the lack of unanimity in the findings, it seemed worthwhile to replicate these studies in another population, using somewhat different study design and analysis. It has been argued that there are hazards in the use of hospital patients as controls in retrospective investigations because such persons may not truly represent the population from which the cases are derived (25). The present study avoids this possible hazard, as special efforts were made to insure that cases and controls came from the same designated population.

An earlier paper (26) utilized this study group to assess the relationship of estrogens to benign breast disease.

Materials and methods

The setting for this investigation was Washington County in western Maryland. Patients who had a benign breast tumor removed from 1968 through 1972 were identified in the file of pathology reports from the county's only general hospital. Because non-whites comprise less than 3 per cent of the county population, cases were limited to white females. The cases admitted to this study included only those who were 20–49 years of age when their breast biopsy procedure was done and who had participated in the 1963 private census of the county. This census, which was conducted by the Johns Hopkins School of Hygiene and Public Health, the National Cancer Institute and the Washington County Health Department, obtained information from more than 98 per cent of the households (27).

In all, 358 cases fulfilled the criteria for inclusion in this study. Of these, 320 were successfully interviewed. The reasons for non-participation are given in table 1. There were only 15 refusals and 21 cases had moved out of the county after their surgery in 1968–1972.

To identify controls from the same population from which the cases were derived, the 1963 census list was used as the sampling frame for their selection. For each case, a control matched for year of age was chosen after a random start. Of the 358 originally selected controls, 23 refused to participate and 65 had moved elsewhere since the 1963 census. Because the cases had to be county residents until 1968 or thereafter to be selected into the study, it was expected that more controls than cases had moved out of the county at the time of interview. Whenever a potential control was not interviewed, another was chosen in the same manner. In this way, cases and their population controls were

TABLE 1

Interviews attempted and completed

Interview status	Cases		Controls	
	No.	%	No.	%
Total selected for interview	358	100	434 (358)*	100 (100)
Not interviewed				
Moved beyond county limits	21	5.8	88 (65)	20.3 (18.2)
Refusals	15	4.2	26 (23)	6.0 (6.4)
Deceased	2	0.6	0 (0)	0 (0)
Total interviewed	320	89.4	320 (270)	73.7 (75.4)

* Originally selected controls in parentheses.

also matched for continued residence in the county and for their willingness to participate in a health survey. The results of this selection process of controls are shown in table 1.

The interviews were conducted in the summer of 1973 by five trained female lay interviewers. To minimize possible interviewer bias, approximately equal numbers of cases and controls were assigned to each interviewer. In addition, the interview form was designed to resemble a general health survey, and the interviewers did not know who was a case and who was a control. All potential participants who still lived in the county were contacted: 4.5 per cent of cases (15 out of 335) and 7.5 per cent of controls (26 out of 346) declined the interviews. It is highly unlikely that this minimal difference biased the results of the study because the percentage of refusals was low in both groups, and refusals were similar to participants with respect to education, residence, smoking history and other pertinent factors.

The cases had either cystic disease, fibroadenoma, or cystic disease with fibroadenoma. There were only 25 cases of the latter and their age distribution was similar to the cases of cystic disease, so they were included with them in the analysis. Cystic disease included fibrocystic disease, chronic cystic mastitis, sclerosing adenosis and papillomatosis.

The date of biopsy was the reference date for each case, and the control matched to that case was given the same reference date. For both cases and controls, information on certain important predisposing factors was limited to occurrences prior to the reference date. These factors included pregnancy history, lactation patterns and menstrual history. The rest of the information from the health survey questionnaire, such as educational history and family income, was coded according to the responses given at the time of interview. Other personal and demographic information was provided by the 1963 census.

When the odds ratio for independent samples and the matched pair method of analysis with appropriate significance tests were used to calculate the relative risks, the results were similar, indicating that the effect of matching was small. For this reason, the odds ratio and the Chi square test for independent samples were used for the analysis.

Pregnancy was defined as any pregnancy which lasted five months or longer.

RESULTS

Interviews were completed on 320 cases and their matched controls. Among the cases, 275 had a diagnosis of cystic disease and 45 had fibroadenoma. As expected, cystic disease was more common in the older age groups, and proportionally more cases of fibroadenoma occurred in the younger age groups. In all, 73.8 per cent of the cystic disease cases were 35–49 years of age, while 71.1 per cent of the fibroadenoma cases were 20–34 years of age.

The adequacy of the control selection procedure was supported by the lack of any

significant differences in cases and controls according to variables which from past studies or a priori reasoning are believed not to be related to benign or malignant breast neoplasms. The results are presented in table 2.

There were four characteristics previously associated with breast cancer in other studies, but for which no significant differences (at $p < .05$) were noted between benign cases and controls in this investigation. The findings are shown in table 3 for cystic disease and fibroadenoma cases. Cases and controls had almost the same mean age at menarche and a similar proportion with a past history of artificial menopause resulting from surgery or radiation therapy. With respect to a maternal history of breast cancer, there were 12 cystic disease cases and only six controls in the study who stated that their mother had a diagnosis of breast cancer. Because of the relatively young age of the study group, only seven cystic disease cases and 11 controls had experienced natural menopause.

There were six factors which differed significantly between benign mastopathy cases and their controls: 1) educational history; 2) family income; 3) residence in 1963; 4) smoking history in 1963; 5) age at first pregnancy; and 6) number of term pregnancies. The distribution of cases and controls by these factors and by type of diagnosis is given in table 4. Information on smoking history in the 1963 census was not collected on persons who were under 16 years of age at the time.

Table 5 lists the crude relative risk for the six factors that differed significantly between benign breast disease cases and their controls. The risks are relative to the

TABLE 2

Distribution of cases and controls by characteristics believed not to be associated with breast neoplasia

Characteristic	Cases	Controls
% with characteristic:		
History of varicose veins	15.9	13.1
History of diabetes mellitus	0	1.5
History of cancer other than breast cancer among 1st degree relatives	26.6	27.5
Mothers who breast fed	33.2	33.3
Offspring who were breast fed	23.0	22.6
Protestant religion	87.9	88.4
History of divorce or separation	19.7	18.1
≥ 15 years of residence in Washington County by 1963	76.9	77.5
≥ 15 years of residence in the same house by 1973	33.8	33.8
History of use of a chemical method (vaginal foam, jelly, cream) of birth control	23.4	21.1
Mean no. with characteristic:		
No. of brothers per participant	1.9	2.1
No. of sisters per participant	1.9	1.9

TABLE 3

Characteristics reported to be associated with breast cancer in other studies, but with no significant differences between cases and controls by type of diagnosis

Characteristic	Cystic disease (n = 275)	Controls (n = 275)	Fibroadenoma (n = 45)	Controls (n = 45)	All cases (n = 320)	Controls (n = 320)
Mean age at menarche	13.2	13.1	12.3	12.6	13.1	13.0
% with artificial menopause	14.9	13.1	2.2	4.4	13.1	11.9
% with natural menopause	2.5	4.0	2.2	2.2	2.5	3.8
% with maternal history of breast cancer	4.4	2.2	4.4	2.2	4.4	2.2

TABLE 4

Percentage with characteristic significantly different between total cases and controls by type of diagnosis

Characteristic	Cystic disease		Fibroadenoma		Total	
	Cases $n = 275$	Controls $n = 275$	Cases $n = 45$	Controls $n = 45$	Cases $n = 320$	Controls $n = 320$
Education (years)						
<11	24.0	32.4	17.8	31.1	23.1	32.2
11-12	58.2	53.8	62.2	53.3	58.8	53.7
13+	17.8	13.8	20.0	15.6	18.1	14.1
Family income						
<$11,000	44.0	53.1	35.6	48.9	42.8	52.5
$11,000+	50.5	37.5	55.6	35.6	51.3	37.2
Not stated	5.5	9.5	8.9	15.6	5.9	10.3
Residence in 1963						
Rural	38.2	49.1	31.1	46.7	37.2	48.8
Urban	37.1	33.5	37.8	35.6	37.2	33.7
Small town	12.4	9.8	11.1	8.9	12.2	9.7
Suburban	12.4	7.6	20.0	8.9	13.4	7.8
Smoked cigarettes by 1963						
No	41.5	57.5	46.7	44.4	42.2	55.6
Yes	54.5	38.9	24.4	28.9	50.3	37.5
Smoking history not obtained (<16 years of age)	4.0	3.6	28.9	26.7	7.5	6.9
Age at first pregnancy						
<21 years old	34.2	48.0	44.4	48.9	35.6	48.1
21+ years old	47.6	34.5	35.6	35.6	45.9	34.7
No pregnancy	18.2	17.5	20.0	15.6	18.4	17.2
No. of term pregnancies						
4+	14.5	22.2	13.3	22.2	14.4	22.2
2, 3	46.9	42.2	48.9	42.2	47.2	42.2
0, 1	38.5	35.6	37.8	35.6	38.4	35.6

first class in each category taken as unity. The cases were better educated and had a higher family income. They were older at the time of their first pregnancy and they had fewer pregnancies. Cases were also less rural in residence and more of them had smoked cigarettes. The benign cases were then separated by type of diagnosis and re-analyzed. Except for smoking history and age at first pregnancy, the findings were similar for cystic disease and fibroadenoma cases, although there were no significant results among fibroadenoma patients, probably due to their small numbers.

Because the association between each of the six significant characteristics and benign mammary tumor can be confounded by the other significant characteristics, simultaneous adjustment for these factors and the past history of estrogen use (26) was accomplished by a binary variable multiple regression method (28). The findings are also presented in table 5. After adjustment, more education, suburban residence, fewer pregnancies and a positive smoking history persisted as important risk factors in relation to the occurrence of a benign tumor, while differences in nulliparity between cases and controls could have arisen by chance ($p = .12$). A high family income was no longer an important factor with respect to benign disease.

When cystic disease and fibroadenoma were analyzed separately after adjustment, education persisted as an important risk factor for cystic disease, but not for fibroadenoma. In turn, family income continued as a noteworthy variable for fi-

TABLE 5

Relative risk (RR) of characteristics significantly different between cases and controls, before adjustment

Characteristic	Cystic disease		Fibroadenoma		All cases	
	Crude RR	Adjusted RR†	Crude RR	Adjusted RR†	Crude RR	Adjusted RR†
Education (years)						
< 11	1.0	1.0	1.0	1.0	1.0	1.0
11-12	1.5	1.6*	2.0	0.8	1.5*	1.5*
13+	1.7	1.8*	2.3	1.1	1.8*	1.8*
Family income						
< $11,000	1.0	1.0	1.0	1.0	1.0	1.0
$11,000+	1.6*	1.0	2.1	1.9	1.7*	1.1
Residence in 1963						
Rural	1.0	1.0	1.0	1.0	1.0	1.0
Urban	1.4	1.0	1.6	1.5	1.4	1.1
Small town	1.6	1.2	1.9	2.3	1.6	1.3
Suburban	2.1*	1.6	3.4	3.5	2.3*	1.8*
Smoked cigarettes by 1963						
No	1.0	1.0	1.0	1.0	1.0	1.0
Yes	1.9*	1.8*	0.8	0.8	1.8*	1.6*
Age at first pregnancy						
<21 years old	1.0	1.0	1.0	1.0	1.0	1.0
21+ years old	1.9*	1.1	1.1	0.9	1.8*	1.1
No pregnancy	1.5	1.6	1.4	0.9	1.4	1.5
No. of term pregnancies						
4+	1.0	1.0	1.0	1.0	1.0	1.0
2, 3	1.7*	3.3*	1.9	1.0	1.7*	2.5*
0, 1	1.7*	4.3*	1.8	1.0	1.7*	3.2*

* Significantly greater than a relative risk of 1.00 at $p < .05$.

† Adjusted for other variables in table, as well as age and past history of estrogen use (26), by Feldstein's method of binary variable multiple regression (28).

broadenoma, but not for cystic disease. Adjustment also removed age at first pregnancy as a risk factor for cystic disease and number of term pregnancies as a risk factor for fibroadenoma.

DISCUSSION

In retrospective (case-control) studies, a major assumption is that diagnosed cases and their controls come from the same defined population. It is usually impossible to be certain that this assumption is correct in hospital-based studies. A major advantage of the present study is that cases and controls are known to have come from the same population, namely persons who were enumerated in the 1963 census of Washington County, Maryland, and who were currently residing in the county and willing to be interviewed.

Part of the rationale for this investigation was related to the possible pre-cancerous nature of cystic breast disease. When the epidemiologic characteristics of cystic and malignant mammary tumors were compared to clarify the relationship between both conditions in the present study, both similarities and dissimilarities were noted in their characteristics.

Cystic disease cases were found to have the following attributes which have been observed in breast cancer cases in many studies: a higher socioeconomic status as manifested by better education; fewer pregnancies; and a lack of association with lactation patterns. More cystic cases than controls were nulliparous and had mothers with breast cancer, although these differences could have occurred by chance.

On the other hand, some of the risk factors associated with breast cancer were not associated with cystic disease in the

present study. Cystic cases did not differ from controls with respect to early menarche, age at first pregnancy, history of artificial menopause, or late natural menopause. The lack of a significant association with late natural menopause may be related to the fact that few women had undergone natural menopause because of the relatively young age of the study population.

Although there was a positive association between those who had ever smoked cigarettes by 1963 and the occurrence of cystic breast disease, there was no evidence of a dose-response effect according to the number of cigarettes smoked daily. This finding suggests that the association of cigarette smoking with cystic mammary disease may well be coincidental rather than causal.

On balance, evidence from this and previous studies indicates more epidemiologic similarities than dissimilarities between cystic breast disease and breast cancer. The high risk of subsequent breast cancer among women with cystic mammary tumor as estimated from clinical studies further supports the view that they are related entities. However, further work needs to be done to characterize in more detail three identifiable groups: 1) women who are at high risk for breast cancer; 2) women who are at high risk for cystic disease; and 3) women with a past history of cystic disease who are at high risk for breast cancer.

Although there were only 45 cases of fibroadenoma, it was of interest to look at its epidemiologic pattern. There was a suggestion that fibroadenomatous cases had a higher socioeconomic status than controls, as reflected by income and suburban residence. However, there were only minimal differences between cases of fibroadenoma and controls by age at first pregnancy, number of term pregnancies, nulliparity, maternal history of breast cancer, age at menarche, history of artificial menopause and age at natural menopause. If these preliminary observations are supported by others, it would suggest that fibroadenoma and breast cancer may be entirely separate entities.

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