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AN EPIDEMIOLOGIC STUDY OF FIBROCYSTIC BREAST DISEASE WITH REFERENCE TO DUCTAL EPITHELIAL ATYPIA

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A case-control study of 255 women with fibrocystic breast lesions and 790 controls was conducted at two hospitals in New Haven, Connecticut during 1977–1979. Cases were found to weigh significantly less than controls, and were more likely than controls to have: a first-degree female relative with a history of breast cancer; a higher level of education; a recent history of regular gynecologic checkups; and (if under age 45 years) a later age at first pregnancy. They were less likely to have had a surgical menopause. The degree of ductal epithelial atypia in breast biopsy specimens was evaluated in order to see whether epidemiologic characteristics differed according to the degree of ductal atypia. The only variable to show a linear relationship with ductal atypia was a recent history of regular gynecologic checkups; those with no or minimal atypia were more likely to have had recent checkups than those with high atypia scores. This study thus gives no evidence that known risk factors for breast cancer are more strongly associated with fibrocystic breast disease with a high degree of atypia than with fibrocystic breast disease with a low degree of atypia. It also provides data to support the belief that women having frequent gynecologic checkups are more likely to be included as cases in case-control studies of fibrocystic breast disease, and particularly in the groups with no or minimal atypia, than those not having frequent checkups.

fibrocystic disease of breast; ductal atypia

Considerable uncertainty still exists about risk factors for fibrocystic breast disease (1–12). Furthermore, the extent to which the epidemiology of fibrocystic disease differs according to histopathologic subtype is not known. Black and Chabon (13) have developed a classification scheme by which biopsy specimens from fibrocystic lesions can be graded according to the degree of epithelial atypia observed in the branching segments of the duct system of the breast. Studies which have used this

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classification (14, 15) have shown that the subsequent risk of developing breast cancer is higher in women with a greater degree of ductal atypia relative to women with little or no atypia present. The present study was initiated to provide further data on the epidemiologic characteristics associated with fibrocystic disease in general and with fibrocystic disease subclassified by extent of ductal atypia. In particular, it was desired to determine whether known risk factors for breast cancer are more strongly associated with fibrocystic breast disease with a high degree of atypia than with fibrocystic disease with no or minimal atypia.

MATERIALS AND METHODS

This case-control study compared characteristics of 255 women aged 20–74 years with a current biopsy-confirmed diagnosis of fibrocystic breast disease who were admitted to two hospitals in New Haven, Connecticut, between November 1977 and May 1979 to characteristics of 790 women admitted to surgical services of the same two hospitals over the same time period for disorders not involving the breast. Approximately 30 per cent of the cases had had at least one breast biopsy prior to the index admission and this was taken into account in the analyses. The study pathologist (V.A.L.), who had no knowledge of the study subjects' exposure to possible risk factors, reviewed all biopsy specimens; only cases classified as fibrocystic breast disease by her were included as cases. The study pathologist also evaluated all specimens according to the classification system of Black and Chabon (13), which involves grading the epithelial lining of each of four groups of breast ducts from 1 (normal) to 5 (extreme disorganization with malignant transformations). The four groups of ducts are 1) primary ducts and their major interlobular subdivisions, 2) terminal interlobular ducts, 3) intralobular ducts, and 4) acini. The average of the four duct grades was then used as an overall measure of ductal atypia. Apocrine change can be graded in a similar manner but, in this study, results were not altered appreciably when apocrine grade was included; therefore, the average of the four duct grades is used in the analyses to be presented here. Cases were subsequently divided into three atypia groups ranging from no/low to high atypia.

Controls were chosen from among patients admitted to the general surgical, orthopedic, or otolaryngologic services of the two hospitals. Controls aged 20–44 years were recruited in a one-to-one ratio with cases within each hospital and were group-matched to cases within five-year age intervals. In the age group 45–74 years, controls were women admitted to these same hospital services who were being included as controls in a concurrent study of exogenous estrogens and female reproductive system cancers (16) in which the same questionnaire was being used. These controls were sampled systematically from hospital daily admission records. Potential cases and controls were excluded if they reported a history of cancer of the breast or other reproductive organs, were non-English speaking, or were not residents of Connecticut. Response rates were 85 per cent for patients with fibrocystic disease and 77 per cent for controls. Refusals included subjects unwilling to be interviewed (8 per cent of cases; 11 per cent of controls) and those whose physicians did not give permission for them to be contacted by study personnel (7 per cent of cases; 11 per cent of controls).

Trained interviewers administered a standardized, structured questionnaire to collect information on variables previously suspected to be risk factors for benign or malignant breast disease, including demographic characteristics, reproductive factors, selected medical history, history of use of oral contraceptives and estrogen replacement therapy, smoking habits, indicators of body build, and mother's and sisters' history of cancer and cause of death. When-

ever a woman was unsure about having used a particular drug of interest or about details of previous surgery on her reproductive system, permission was sought to request such information from her physician(s) or hospital. This was necessitated for a similar proportion of cases and controls. Subjects were interviewed in the hospital whenever possible (60 per cent of cases and 69 per cent of controls) and at home or occasionally elsewhere otherwise.

Following preliminary bivariate analyses, linear logistic regression analysis (17) was used to examine the association between possible risk factors and fibrocystic disease in general while taking into account effects of other risk factors. When the three atypia groups were considered, log-linear models were constructed using the program "FREQ", developed by Haberman (18). Since the design matrix is submitted by the user in this program, all variables including dependent ones may appear in a continuous or multi-categorical format.

RESULTS

Table 1 shows that while the age distributions of cases and controls below age 45 years are similar, the distributions differ substantially above this age. Therefore, data were age-adjusted when subjects of age 45 years or older were included in analyses.

TABLE 1

Distribution of cases of fibrocystic disease and controls by age: case-control study at two hospitals in New Haven, Connecticut, 1977–1979

Age (years)	Cases		Controls	
	No.	%	No.	%
20–24	4	1.5	4	0.5
25–29	12	4.7	13	1.6
30–34	21	8.2	23	2.9
35–39	51	20.0	52	6.6
40–44	37	14.5	37	4.7
45–49	53	20.8	93	11.8
50–54	32	12.5	137	17.3
55–59	19	7.5	142	18.0
60–64	14	5.5	112	14.2
65–69	8	3.1	85	10.8
70–74	4	1.7	92	11.6
Total	255	100.0	790	100.0

Characteristics of all fibrocystic disease will be reported first followed by characteristics of cases subdivided according to ductal atypia score.

Fibrocystic disease not subclassified by ductal atypia score

Odds ratios adjusted for age by linear logistic regression are presented in table 2 for selected variables. Elevated odds ratios for fibrocystic disease are seen for women who had a mother or sister with breast cancer, had more than a high school education, had regular checkups during the three years before the interview, and had a later age at first pregnancy. This latter association was only observed for cases and controls younger than age 45 years. Also, the relationship with age at first live birth was similar to that for age at first pregnancy.

A decreased occurrence of fibrocystic disease was modestly associated with increasing weight (and with increasing Quetelet's index (weight/height^2)), but only for women below age 55 years (odds ratio (OR) = 0.8 for each 10 lb (22 kg) increase in weight, age <55 years; OR = 1.0, age ≥55 years). Also, cases were less likely than controls to have had an oophorectomy (OR = 0.5, 95% confidence interval (CI) = 0.3–0.9). A decreased occurrence of fibrocystic disease among subjects under age 45 years was associated with ever having used oral contraceptives; further details on the use of oral contraceptives in this population are presented elsewhere (19). Cases and controls generally had similar numbers of pregnancies, live births, miscarriages, abortions, and stillbirths, as well as similar ages at natural menopause. Also, no meaningful differences were observed for the variables listed in the footnote to table 2. When linear logistic regression analysis was used to control for possible confounding by variables other than age, none of these associations were appreciably altered. No other statistical interactions were identified, apart from those mentioned above.

TABLE 2

Distribution of cases and controls by selected variables, and odds ratios and 95% confidence intervals for associations between variables and fibrocystic disease: case-control study of two hospitals in New Haven, Connecticut, 1977–1979*

Variable	% cases (n = 255)	% controls (n = 790)	Odds ratio	95% confidence interval
History of mother or sister with breast cancer				
Yes	34.7	20.0	2.8	1.5–5.3
No	65.3	80.0		
Education				
>High school	36.5	22.0	1.8	1.3–2.5
≤High school	63.5	78.0		
Recent history of regular checkups†				
Yes	80.4	59.7	1.8	1.3–2.7
No	19.6	40.3		
Ever pregnant				
Yes	85.6	84.3	1.0	0.6–1.6
No	14.4	15.7		
Mean age (years) at first pregnancy‡	23.40	21.75	1.7 for each 5-year increase	1.2–2.4
Mean age (years) at menarche	12.98	12.74	1.1 for each 3-year increase	0.8–1.4
Mean no. of abortions, miscarriages	0.59	0.62	0.9 for each non-live birth	0.8–1.5
Mean no. of livebirths	2.95	2.81	1.1 for each live-birth	0.9–1.7
Mean weight (lb or kg)	136.20 lb (300.27 kg)	147.22 lb (324.56 kg)	0.8 for each 10 lb (22 kg) increase	0.7–0.9
Mean age (years) at menopause (excluding subjects with surgical menopause)	47.45	47.31	1.1 for each 5-year increase	0.8–3.0
Had surgical menopause§				
Yes	8.3	16.1	0.6	0.4–1.0
No	91.7	83.9		

* Age adjusted by linear logistic regression. The following variables had odds ratios of approximately unity and were not statistically significantly associated with fibrocystic disease: race, religion, marital status, respondent's birthplace, mother's birthplace, father's birthplace, use of hormones to dry up breasts, blood clots in veins or lungs, varicose veins, diabetes, thyroid disease, irregular menstrual cycles, low back pain, hypertension, birth control method excluding oral contraceptives, and smoking history. In addition, a slight negative association between ever having breast fed and fibrocystic disease was no longer significant when controlling for the associations between factors in this table and fibrocystic disease.

† "Regular checkups" defined as undergoing annual or semi-annual gynecologic exams during the three years preceding interview.

‡ For ages less than 45 years only; above age 44 years, mean for cases = 24.5, mean for controls = 24.1, $p > 0.05$.

§ Both ovaries removed.

Since it was recognized that a woman with a history of benign breast disease prior to the current diagnosis (31 per cent of cases) may have altered certain exposures or health behavior patterns because of the disease, the aforementioned age-adjusted analyses were repeated after excluding these cases. Only one relatively modest difference was found, in that a history of breast cancer in a first-degree female relation was a stronger risk factor for cases with previous benign breast disease than in those without a history of benign breast disease (OR = 2.8, 95% CI = 1.5–5.3 vs. OR = 2.0, 95% CI = 0.9–4.6).

Fibrocystic disease subclassified by ductal atypia score

The frequency distribution of the fibrocystic disease cases by their mean ductal atypia score is shown in table 3. As found in other studies using this classification (14, 15), the majority of cases had either no evidence of atypia or low atypia scores. Cases were divided into three groups according to their mean score: no or minimal atypia (1.00–1.49); intermediate atypia (1.50–1.99); and high atypia (≥2.00). The mean ages of the cases in the three groups were similar; however, the percentage of cases below age 45 years was somewhat greater for cases with no/low atypia than for the intermediate and high groups (53, 39, and 46 per cent, respectively). No differences were observed in the proportions of cases in the three groups who had only the right, only the left, or both breasts biopsied.

TABLE 3

Distribution of fibrocystic disease cases by mean ductal atypia score: case-control study at two hospitals in New Haven, Connecticut, 1977–1979

Mean ductal atypia score	No.	%	
1.00–1.24	75	29.4	No or minimal atypia
1.25–1.49	84	32.9	
1.50–1.74	37	14.6	Intermediate atypia
1.75–1.99	25	9.8	
2.00–2.24	13	5.1	High atypia
2.25–2.49	10	3.9	
2.50–2.74	9	3.5	
2.75+	2	0.8	
Total	255	100.0	

Table 4 indicates that cases in all three atypia groups were more likely than controls to have a recent history of regular gynecologic checkups and that there was a significant inverse relationship between a recent history of regular checkups and atypia level ($p = 0.03$).

While all three atypia groups had a mean weight less than that of the control group (147 lb (324.6 kg)), cases with intermediate atypia had a slightly lower mean weight (134 lb (295.4 kg)) than the other two groups (137 lb (302 kg) for no/low atypia and 137 lb (302 kg) for high atypia). The only other variable found to exhibit any difference among ductal atypia groups was use of oral contraceptives, where the proportion of cases ever having used oral contraceptives was smaller than controls only in the low and intermediate atypia groups (19). No linear pattern of odds ratios was identified when associations between ductal atypia score and the following variables were examined: age at menarche, age at menopause, age at first birth, oophorectomy status, body build, country of birth, race, and family history of breast cancer.

In order to control for potentially confounding variables, including demographic characteristics and reproductive and medical history variables, and also to investigate whether odds ratios of the three atypia groups conformed to a linear or quadratic trend, log-linear modeling was used. In these analyses, it was again found that cases were increasingly more likely than controls to have had regular gynecologic examinations as the ductal atypia score decreased. When this association was controlled for, no other potential risk factor for fibrocystic disease had a significant linear relationship with ductal atypia. Odds ratios did not conform well to a quadratic fit for any variable.

TABLE 4

Frequency distribution and odds ratios for associations of history of regular checkups with each mean ductal atypia group: case-control study of fibrocystic breast disease at two hospitals in New Haven, Connecticut, 1977–1979*

	Yes	No	Total	Odds ratio†
Cases, by mean ductal atypia group				
No or low atypia	133	26	159	3.4
Intermediate atypia	49	13	62	2.4
High atypia	23	11	34	1.4
Controls‡	471	318	789	–
TOTAL	676	368	1,044	

* "Regular checkups" defined as undergoing annual or semi-annual gynecologic exams during the three years preceding the interview.

† Test for linear trend = 4.52, $p = 0.03$.

‡ Referent group.

DISCUSSION

Selection of cases in this study was limited to women seen at a hospital for a breast biopsy or surgical excision of a breast mass. This sample is thus not representative of all women who have fibrocystic disease, some of whom do not receive medical care and others of whom may not be referred to a surgeon even if they do seek care. That all women with fibrocystic disease do not have their conditions diagnosed is clearly supported by autopsy studies (20, 21) in which a high proportion of so-called "clinically normal breasts" have been found to exhibit fibrocystic changes. Indeed, the results of this study indicate that women having regular checkups are more likely to have fibrocystic disease diagnosed and that cases with less ductal atypia are more likely than others to have had regular gynecologic checkups. This suggests that a selection bias may indeed exist in case-control studies which ascertain subjects who have had a biopsy; that is, women with no or minimal atypia are more likely to be included if they have regular checkups, while women with high atypia may be as likely to be included if they do not have regular checkups as if they do. It is thus possible that similarities or differences found among cases with varying degrees of atypia may at least in part reflect this underlying detection bias. The extent to which this bias will affect risk estimates remains in question. If, for example, risk factor exposure does vary with atypia, and exposed subjects undergo more checkups than those unexposed, the association between the exposure and advancing atypia would be more difficult to detect. The present findings suggest that this influence may be modest since the purported risk factors studied were not found to vary linearly with ductal atypia. In any event, it is clear that future research must collect more complete information from cases about factors related to detection, including: frequency of gynecologic examinations; breast self-examination; breast symptoms including pain, swelling, and tenderness; and other factors which could precipitate a biopsy being taken. Investigators need a better understanding of what influences a physician to request that a biopsy be performed. One presumed "influence" is suspicion of cancer which, in itself, may produce a bias toward systematically identifying cases of fibrocystic disease whose clinical presentation, or risk factor profile, may more closely resemble that of a breast cancer patient.

On the other hand, from a physiologic perspective, the finding that cases with greater atypia are less likely to have had regular gynecologic checkups could suggest

that ductal atypia will, in some cases, advance naturally to more florid states when no medical intervention occurs. This theory of "progression" receives some support from the finding that high mean ductal atypia is strongly correlated with certain histopathologic characteristics which are known to form palpable lesions, including gross cysts (22), which might provide the impetus for seeking medical advice. Additionally, cases with no/low atypia were somewhat younger than other cases at diagnosis. For this reason, too, it would be useful in future studies to inquire of women with fibrocystic disease how their condition was first detected and at what age, as well as whether they practiced breast self-examination routinely before diagnosis.

The importance of how fibrocystic disease is detected in the individual is underscored by the finding in this study and in others (5, 8) that thinner women are more likely to have biopsy-confirmed fibrocystic disease than heavier women. Since no plausible biologic mechanism for a protective effect of obesity on fibrocystic disease has been proposed to date, it remains likely that this association is a result of a detection bias; that is, heavier women are less likely to have breast lesions diagnosed because of the greater amount of adipose tissue present in their breasts.

With respect to the reproductive variables studied, the lack of association of fibrocystic disease with age at menarche, nulliparity, and number of livebirths seems to support the findings of most other case-control studies (23). The positive association with age at first pregnancy among younger women is supported by some case-control research (3, 7), but not by other studies (1, 4, 5, 8, 9), while failure to observe a trend of this variable with ductal atypia was recently reported from a cohort study which also used the Black and Chabon classification system (24). It remains difficult, however, to compare findings across studies as a result of differences in diagnostic criteria for cases and methods of data collection.

The existence of previously diagnosed benign breast disease among approximately 30 per cent of the case group raises the question of whether these women, with or without the advice of a physician, may have altered their exposure to putative risk factors or made detailed inquiry into their family history of breast disease, thus biasing certain comparisons. For instance, the finding that cases with pre-existing benign breast disease were significantly more likely to report a family history of breast cancer than newly diagnosed cases may be due to a reporting bias or may have other possible explanations. One explanation is that women with a family history of breast cancer are at increased risk for recurrences of fibrocystic disease; another is that women with a suspected higher risk of breast disease will be under greater medical surveillance. It would be useful to learn from future studies if knowledge of a family history of breast cancer preceded or followed a case's own initial diagnosis of fibrocystic disease. Increased understanding about how newly diagnosed cases differ from prevalent cases may help reconcile findings from previous studies, only some of which were limited to newly diagnosed fibrocystic disease.

The failure to observe linear associations of ductal atypia with nearly all known risk factors for breast cancer, such as reproductive variables, body build and demographic characteristics, is in general agreement with the recent findings of Kampert et al. (25). This indicates that while the Black and Chabon classification may have some value as a prognostic index for determining a woman's risk for breast cancer, the reasons that some women develop fibrocystic breast disease with high atypia seem to be unrelated to known breast cancer risk factors.

The possibility that misclassification of ductal atypia scores occurred was examined by assessing the reliability of the study

pathologist. Inter-observer reliability was evaluated with the assistance of a medical resident in pathology who examined a 10 per cent sample of slides, randomly selected and with a range of atypia scores. Intra-observer reliability was assessed by providing the study pathologist another 10 per cent random sample of slides, without her knowing which ones had been previously read. Both measures of reliability were found to be in a similar range and were quite good; for both measures, agreement was found to range from a Kappa statistic of 0.76 to 1.0, depending on the duct division tested.

In conclusion, this investigation does not support the theory that an increasing level of epithelial ductal atypia in fibrocystic lesions is associated with known risk factors for malignant breast disease. Future studies which include large numbers of cases with advanced epithelial atypia and which thoroughly account for the role of diagnostic factors may clarify the epidemiology of fibrocystic breast disease, increase our understanding of the role of specific histopathologic characteristics, and help us to better understand the relationship between benign and malignant breast diseases.

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