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Risk Factors for Benign Breast Disease according to Histopathological Type: Comparisons with Risk Factors for Breast Cancer

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We evaluated risk factors for benign breast disease by using a case-control study method. The series was taken from participants in breast cancer screening programs during 1978–1986 in Miyagi Prefecture, Japan. All benign breast lesions diagnosed during this period were reviewed and reclassified into proliferative and non-proliferative types based on the Dupont and Page classification. Data on 382 benign breast disease cases (130 proliferative-type cases and 252 non-proliferative-type cases) and 1,489 screening year-, age- and screening area-matched normal controls were used for analysis. Nulliparity or low parity and family history of breast cancer in mother or sisters were significantly associated with an increased risk of proliferative type. Premenopausal status was significantly associated with an increased risk of non-proliferative type. No significant association with history of lactation for the last child was observed in either type, but the risk of proliferative type increased with increasing duration of lactation (P=0.08). A comparison between the present findings and the risk factors for breast cancer indicated epidemiologic similarities between proliferative benign and malignant breast lesions in general. The associations of these two lesions with lactation patterns were, however, dissimilar.

Key words: Benign breast disease — Breast cancer — Risk factors

Many epidemiologic studies of breast cancer have shown that a history of benign breast disease (BBD) increases the risk of breast cancer.[1–4] An excess risk of developing breast cancer among women with BBD has been demonstrated, mainly based on retrospective cohort studies that followed women with biopsy-defined BBD.[5–8] In addition, most studies found that the magnitude of the risk varies according to the histopathological type. Thus, it seems important to identify risk factors for BBD according to histopathological type and to compare them with those for breast cancer, in order to cast light on the relationship between two conditions.

However, in contrast to the many epidemiologic studies of breast cancer, there have been few of BBD.[9–21] Furthermore, there are remarkable inconsistencies among the results of these epidemiologic studies of BBD, possibly because of differences in histopathological classification and the relatively small sample sizes of the studies.[22, 23] Recently, Dupont and Page proposed a standardized histopathological classification of BBD, which is widely accepted.[6, 24–26] Several studies have already reported the risk of breast cancer among women with BBD, based on this classification.[6, 27–30]

In this study, we evaluated risk factors for BBD according to histopathological type, using the Dupont and Page classification, and compared them with those for breast cancer. Study subjects were selected from participants in breast cancer screening programs and a case-control study method was applied.

MATERIALS AND METHODS

Study subjects The series in this study consisted of participants in breast cancer screening programs during 1978–1986 in Miyagi Prefecture, Japan. The screening was conducted as follows. The conventional first-stage screening consisted of clinical breast examination, e.g., inspection and palpation, of the breasts and the regional lymph nodes. Smear cytology was performed on subjects with abnormal nipple discharge. Subjects with any abnormal findings detected by clinical breast examination, and those with abnormal cytologic features (class II to V) entered the second stage of screening with film mammography and ultrasonography. The women requiring aspiration biopsy cytology and surgical biopsy were referred to community hospitals.

During the screening period, a total of 172,015 women participated in the breast cancer screening and a total of 678 women underwent surgical biopsy at community referral hospitals. Among them, 107 biopsies were diagnosed as breast cancer, and the remaining 571 biopsies were diagnosed as benign at 47 referral hospitals. Since 34 biopsies were derived from 17 women (double biopsies), only the first biopsy was taken for the purpose of this study. Consequently, 554 women were selected as candidates for cases in this study. In 1991, we attempted to collect the relevant slides from the various hospitals for

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review. We found that 164 slides for 164 women were missing, so that 390 cases were available. For each case, 4 controls were randomly selected from among women who had attended the screening program in the same municipality and were diagnosed as normal, matching for age (±2 years) and the year of the screening. But, only one control in 8 cases, 2 controls in 5 cases and 3 controls in 5 cases were eligible. No eligible controls were found in 5 cases. In total, 1,489 controls were selected.

Information on reproductive history (age at menarche, age at first birth, age at last birth, history of abortion, number of parity, history of lactation for the last child and age at menopause) and medical history (histories of benign breast disease and gynecologic disease and family history of breast cancer) has been routinely collected from all screening participants. Before the first-stage screening, public health nurses interviewed the screenees and entered the above information in their medical records. Data on study subjects were obtained from these records.

Histopathological classification Three hundred and ninety slides with the first BBD diagnosis were reviewed and reclassified by two of the authors (Y. T. and N. O.). Histopathological diagnosis was made according to the classification of Dupont and Page.[24–26] The frequencies of diagnoses in the 390 cases are shown in Table I. Three cases with a diagnosis of carcinoma *in situ* were excluded from subsequent investigation. Five cases mentioned above, for which no eligible controls were found, were also excluded: those included proliferative disease without atypia (one case), fibroadenoma (two cases) and fibrocystic change (two cases). Consequently, 382 pairs (382 cases and 1,489 controls) were available for data analysis.

For analysis, all study subjects were regrouped into two major categories according to epithelial proliferation of BBD, i.e. (1) proliferative type including atypical hyperplasia, and proliferative disease without atypia and (2) non-proliferative type including fibrocystic change, fibroadenoma, lipoma and panniculitis.

Statistical analysis Data analyses were performed by using a conditional logistic regression model.[31] In the analyses, age at menarche, age at first birth, age at last birth and number of parity were each categorized into four groups, and age at menopause was categorized into three groups, with surgical menopause as the missing value. The odds ratios for each level versus the reference level were calculated along with the 95% confidence intervals. Adjusted odds ratios were also calculated using the multivariate conditional logistic regression model, and the independent effect of each variable was evaluated. For variables categorized into three or four groups, the linear relation of the variable was tested as a trend across the categories by testing the significance of the single variable coded as the category of exposure. Analyses were carried out for two major categories, proliferative and non-proliferative types, respectively. The mean age of the cases of proliferative type was 44.1±7.3 (SD) years, and that of cases of non-proliferative type was 45.8±9.1 (SD) years. The cases of proliferative type were younger than those of non-proliferative type (P=0.05).

RESULTS

Odds ratio and 95% confidence interval of each study variable according to histological type are presented in Table II. Family history of breast cancer in mother or sisters was associated with an increased risk of proliferative-type BBD. Increasing number of parity, the risk of proliferative-type BBD decreased. On the other hand, premenopausal women had an increased risk of non-proliferative-type BBD. The direction of the effect of age at menopause, though not significant, was inverse between proliferative and non-proliferative types. No association with age at menarche was observed ineither type.

The variables, which have been known to be associated with breast cancer risk, were entered into a multivariate conditional logistic regression model and adjusted odds

Table I. Distributions of 390 Benign Breast Disease Cases during 1978–1986

Age (years)	Proliferative type		Non-proliferative type3			DCIS	Total
	AH	PDWA	FCC	FA	Others		
–39	2	32(1)	41(2)	29(1)	0	0	104(4)
40–49	11	65	77	27(1)	5	1(1)	186(2)
50–59	3	14	40	11	7	2(2)	77(2)
60–	1	3	9	7	3	0	23
Total	17	114(1)	167(2)	74(2)	15	3(3)	390(8)

( ) Number of cases excluded from the analysis. AH, Atypical hyperplasia; PDWA, proliferative disease without atypia; FCC, fibrocystic change; FA, fibroadenoma; Others, panniculitis or lipoma; DCIS, ductal carcinoma *in situ*.

Table II. Crude Odds Ratios and 95% Confidence Intervals according to Histopathological Type, for Reproductive Factors and Family History Associated with Benign Breast Disease Risk for Participants in Breast Cancer Screening, Miyagi Prefecture, Japan, 1978–1986

	Proliferative type 130 pairs				Non-proliferative type 252 pairs			
	No. of cases	No. of controls	Odds ratio	95% confidence interval	No. of cases	No. of controls	Odds ratio	95% confidence interval
Age at menarche (years)								
≤13	41	157	1.00		65	267	1.00	
14	34	142	0.94	0.56–1.57	76	256	1.22	0.83–1.79
15	36	116	1.23	0.70–2.15	52	228	0.94	0.61–1.46
16≤	18	91	0.78	0.39–1.53	55	227	0.97	0.60–1.58
				Trend P=0.79				Trend P=0.68
Age at first birth (years)								
≤24	59	266	1.00		133	508	1.00	
25≤ ≤29	50	193	1.20	0.77–1.86	86	381	0.86	0.63–1.17
30≤	6	30	1.03	0.39–2.69	16	45	1.40	0.76–2.58
Nulliparous	11	17	3.27	1.37–7.78[b)]	10	44	0.83	0.40–1.73
				Trend P=0.03[b)]				Trend P=0.81
Age at last birth (years)								
≤29	77	279	1.00		140	529	1.00	
30≤ ≤34	34	180	0.67	0.42–1.07	74	330	0.84	0.61–1.16
35≤	5	26	0.66	0.24–1.85	22	70	1.14	0.66–1.98
Nulliparous	11	17	2.50	1.06–5.90[b)]	10	44	0.81	0.39–1.68
				Trend P=0.52				Trend P=0.64
History of abortion								
Absent	64	217	1.00		122	450	1.00	
present	62	280	0.76	0.51–1.15	117	520	0.83	0.62–1.11
Number of parity								
0	11	17	1.00		10	44	1.00	
1	9	50	0.27	0.09–0.81[b)]	27	89	1.35	0.59–3.09
2	69	252	0.39	0.17–0.94[b)]	120	445	1.24	0.60–2.57
3≤	38	186	0.29	0.12–0.69[b)]	88	402	0.94	0.44–1.98
				Trend P=0.03[b)]				Trend P=0.23
Lactation for the last child								
Never	21	79	1.00		42	141	1.00	
Ever	93	407	0.83	0.48–1.44	194	789	0.85	0.57–1.25
Nulliparous	11	17	3.03	1.16–7.88[b)]	10	44	0.76	0.34–1.66
Menopausal status								
Postmenopausal	21	91	1.00		48	254	1.00	
Premenopausal	102	373	1.68	0.68–4.15	181	656	2.22	1.24–3.97[b)]
Surgical menopause[a)]	7	43			23	72		
Age at menopause (years)								
≤49	11	54	1.00		22	123	1.00	
50≤ ≤54	9	36	1.25	0.39–4.03	25	124	0.87	0.41–1.81
55≤	1	1	4.75	0.26–87.90	1	7	0.49	0.05–4.88
				Trend P=0.46				Trend P=0.55
Family history of breast cancer								
Absent	122	499	1.00		240	956	1.00	
Present	8	8	4.31	1.55–11.95[b)]	12	26	1.80	0.90–3.59

a) Surgical menopause was treated as a missing value in the logistic model.
b) Statistically significant at P<0.05.

ratios were estimated. Since the subjects with nulliparity in the categories of age at first birth, age at last birth, number of parity and lactation consisted of the same nulliparous women, number of parity was entered into the model. The adjusted odds ratios are shown in Table III. Associations with number of parity and family history of breast cancer were evident in the proliferative type.

The effect of parity was further examined using another multivariate logistic regression model. "Number of parity" was regrouped into two categories (nulliparous and par-

Table III. Adjusted Odds Ratios and 95% Confidence Intervals for Reproductive Factors and Family History Associated with Benign Breast Disease Risk Estimated by Multivariate Analysis for Participants in Breast Cancer Screening, Miyagi Prefecture, Japan, 1978–1986

Factors	Proliferative type 130 pairs		Non-proliferative type 252 pairs	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Age at menarche (years)				
≤13	1.00		1.00	
14	0.99	0.58–1.70	1.22	0.83–1.81
15	1.35	0.76–2.40	0.94	0.60–1.46
16≤	0.93	0.47–1.85	0.99	0.61–1.61
	Trend P=0.82		Trend P=0.71	
Number of parity				
0	1.00		1.00	
1	0.29	0.09–0.87[a)]	1.42	0.61–3.27
2	0.39	0.16–0.93[a)]	1.26	0.60–2.64
3≤	0.29	0.12–0.70[a)]	0.94	0.44–2.02
	Trend P=0.03[a)]		Trend P=0.20	
Family history of breast cancer				
Absent	1.00		1.00	
Present	4.13	1.46–11.71[a)]	1.95	0.96–3.94

a) Statistically significant at $P<0.05$.

Table IV. Adjusted Odds Ratios and 95% Confidence Intervals for Lactation Associated with Benign Breast Disease Risk Estimated by Multivariate Analysis among Parous Women in Breast Cancer Screening Participants, Miyagi Prefecture, Japan, 1978–1986

	Proliferative type 119 pairs				Non-proliferative type 242 pairs			
	No. of cases	No. of controls	Odds ratio[a)]	95% confidence interval	No. of cases	No. of controls	Odds ratio[a)]	95% confidence interval
Lactation for the last child								
Never	21	79	1.00		42	141	1.00	
Ever	93	407	0.88	0.48–1.59	194	789	0.96	0.63–1.45
Duration of lactation for the last child (months)								
Never	21	9	1.00		42	141	1.00	
≤6	36	190	0.63	0.33–1.23	73	318	0.89	0.57–1.39
7≤ ≤12	23	104	1.01	0.47–2.16	53	198	1.08	0.65–1.81
13≤	34	113	1.55	0.75–3.22	68	273	1.02	0.62–1.67
				Trend P=0.08				Trend P=0.74
Sufficiency of milk for the last child								
Never	21	79	1.00		42	141	1.00	
Insufficient	31	123	0.97	0.49–1.91	55	232	0.95	0.58–1.54
Sufficient	61	282	0.85	0.45–1.58	139	556	0.96	0.62–1.47

a) Odds ratios were adjusted for age at menarche, age at first birth, age at last birth, number of parity and family history of breast cancer.

Table V. Odds Ratios and 95% Confidence Intervals for Reproductive Factors, Family History and Lactation Associated with Breast Cancer Risk for Participants in Breast Cancer Screening, Miyagi Prefecture, Japan, 1987–1991[a)]

Factors	Breast cancer 204 pairs		Odds ratio	95% confidence interval
	No. of case	No. of controls		
Age at menarche (years)				
≤13	56	210	1.00	
14	48	192	0.92	0.59–1.42
15	55	179	1.08	0.69–1.71
16≤	44	226	0.66	0.40–1.08
			Trend P=0.19	
Age at first birth (years)				
≤24	86	401	1.00	
25≤ ≤29	78	313	1.22	0.86–1.73
30≤	20	45	2.08	1.16–3.71[c)]
Nulliparous	16	41	1.85	0.95–3.64
			Trend P=0.01[c)]	
Age at last birth (years)				
≤29	95	404	1.00	
30≤ ≤34	62	277	0.96	0.66–1.39
35≤	26	79	1.45	0.86–2.46
Nulliparous	16	41	1.69	0.86–3.33
			Trend P=0.10	
History of abortion				
Absent	97	385	1.00	
Present	96	397	0.96	0.70–1.32
Number of parity				
0	16	41	1.00	
1	24	67	0.93	0.44–1.95
2	84	346	0.64	0.34–1.20
3≤	78	353	0.57	0.31–1.06
			Trend P=0.03[c)]	
Menopausal status				
Postmenopausal	85	382	1.00	
Premenopausal	94	351	2.08	1.02–4.22[c)]
Surgical menopause	24	70		
Age at menopause (years)				
≤49	29	146	1.00	
50≤ ≤54	50	213	1.14	0.66–1.99
55≤	6	23	1.60	0.55–4.67
			Trend P=0.43	
Family history of breast cancer				
Absent	195	790	1.00	
Present	9	20	1.80	0.81–4.00
Lactation[b)]				
Never	37	106	1.00	
Ever	146	660	0.61	0.39–0.95[c)]
Duration of lactation for the last child (months)[b)]				
Never	37	106	1.00	
≤6	47	232	0.53	0.30–0.84[c)]
7≤ ≤12	47	200	0.68	0.39–1.17
13≤	52	228	0.71	0.42–1.18
			Trend P=0.55	
Sufficiency of milk for the last child[b)]				
Never	37	106	1.00	
Insufficient	33	149	0.61	0.35–1.06
Sufficient	115	511	0.64	0.41–1.01

a) Abstracted from tables in Minami *et al.*[4)]
b) Reanalysis for 188 parous pairs. Odds ratios were adjusted for age at menarche, age at first birth, age at last birth, number of parity and family histry of breast cancer.
c) Statistically significant at $P<0.05$.

ous) and the effect of nulliparity was re-evaluated. The risk for nulliparous women compared with parous women significantly increased in proliferative type (odds ratio 3.01, 95% CI 1.29–7.01); in non-proliferative type, the odds ratio for nulliparity was 0.86 (95% CI 0.42–1.79) (data not shown in the table).

The risk of BBD associated with lactation was examined based on the history of lactation for the last child. Age at menarche, age at first birth, age at last birth, number of parity, family history of breast cancer and lactation were entered into the regression model, and the adjusted odds ratios for factors relating to lactation were calculated. As shown in Table IV, there was no association between history of lactation itself and the risk of BBD in either histopathological type. However, in the case of proliferative type, the odds ratio increased with increasing duration of lactation (*P* for trend=0.08), which is in contrast with the case of the non-proliferative type.

DISCUSSION

One of the general problems in epidemiological studies of BBD is that the benign lesions which are biopsied represent only a portion of all such lesions in the study population. Since BBD is a very common condition in women, the cases in the studies might include the most clinically significant lesions.[22, 23, 32] In our study, the study subjects were selected from the participants in breast cancer screening programs and the differential diagnoses between cases and controls were based on the standardized screening manual. Therefore, the study population is represented by the study subjects selected and the comparison of cases and controls in this study setting seems reasonable.

The major limitation of this study is probably that 164 women, whose slides were missing, were excluded from the analyses. Comparing the 164 excluded women with the 390 cases, the mean age of the excluded women (45.2 years) was similar to that of the cases (45.1 years). Furthermore, there was no difference in prognosis between the excluded women and the cases, as measured in terms of the cumulative rate of breast cancer development during 1979–1992 (unpublished result). Taking these facts into consideration, it is not likely that there is a big difference in characteristics between the 164 excluded women and the 390 cases.

The present study examined risk factors for BBD based on the histopathological classification proposed by Dupont and Page. We found some characteristics to be associated with the risk of BBD. Low parity and family history of breast cancer significantly and independently increased the risk of proliferative-type BBD. Premenopausal women had a significantly higher risk of non-proliferative type than women with menopause. In parous women, the risk of proliferative type increased with increasing duration of lactation for the last child. Similar findings have been reported in previous studies.[10, 11, 13, 17–19, 21] It is difficult, however, to make direct comparisons among the studies because of the differences in the histopathological classification and terminology employed.[9–21] Histopathological categories used in previous studies include such diverse terms as cystic disease, chronic cystic disease, fibrocystic disease, fibroadenoma, mammary dysplasia, hyperplasia and sclerosing adenosis. The histopathological classification systems are not completely comparable. Although it seems that these studies have revealed the general epidemiological characteristics of BBD, direct comparisons of the findings should be avoided.

We have already reported that a history of BBD was associated with an increased risk of screen-detected breast cancer.[4] Several other studies reported that women with proliferative BBD had an excess risk of breast cancer development.[5–8, 27–30] These findings indicate that the presence of proliferative BBD might be an important prognostic sign for subsequent breast cancer development. Accordingly, we compared the present findings with the risk factors for breast cancer in our previous study, which convered 204 screen-detected breast cancer cases[4] (Table V). Family history of breast cancer in mother or sisters was associated with an increased risk of proliferative BBD and of breast cancer. Premenopausal status was associated with an increased risk of non-proliferative BBD and of breast cancer. Increasing number of parity decreased the risks of proliferative BBD and breast cancer. Thus, our consecutive studies showed that women with proliferative BBD share major breast cancer risk factors. Furthermore, the mean age of women with breast cancer (52.6 years) was greater than that of women with proliferative BBD (44.1 years). These results suggest that there is a similarity in etiologic factors between proliferative BBD and breast cancer and that a part of the benign lesions may progress to malignant lesions. Actually, in our study population, the risk of breast cancer development among women with proliferative BBD was significantly elevated (unpublished result). However, among several BBD risk factors, the magnitude of the odds ratios for family history of breast cancer and low parity was larger than that in breast cancer, and the association with lactation for the last child was different from that of breast cancer; in breast cancer, lactation for the last child significantly reduced risk and no trend of the risk associated with duration of lactation was observed (*P*=0.55). In the progression from normal breasts to proliferative lesions, family history and low parity may play more important roles. Concerning lactation, similar results to ours have been reported in other studies on BBD.[12, 16] Although the choice of lactation practice might be influenced by lifestyle factors, breast function itself might be a determinant

of prognosis, i.e. benign or malignant, in breast diseases. It seems that the role of breast function in the etiology of breast diseases should be considered.

Among the comparisons mentioned above, the findings relating to menopausal factors may be influenced by selection bias, because surgical menopausal women were excluded from the analysis. Moreover, since the study subjects were relatively young in the present study, the number of subjects might have been too small to allow precise estimation of the effect of age at menopause. However, the differences in risk between two benign histopathological types and the similarity in the association with age at menopause between proliferative BBD and breast cancer could not be entirely explained by selection bias. The situation requires further examination.

In this study, the risk factors for BBD by age group were not evaluated. On the other hand, the risk factors previously reported for breast cancer varied between early and late onsets. Family history of breast cancer in mother or sisters and lactation were associated with early onset, and number of parity was related to late onset.[4] Since aging seems an important factor in the etiologies of breast diseases, there may be differences in the relation between BBD and breast cancer among age groups. The evaluation of age-specific risk factors is needed in future studies. To our knowledge, no epidemiological study of risk factors using the Dupont and Page classification has yet been published, except for this study. Additional studies using the same classification may lead to both the resolution of inconsistencies between previous epidemi-ological studies and the clarification of the etiologies of BBD and breast cancer.

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