Benign Breast Disease as a Breast Cancer Risk in Japanese Women

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A hospital-based retrospective cohort study of benign breast disease (BBD) as a risk factor of future breast cancer (BC) development was conducted. Four hundred and twenty-eight patients with biopsied BBD were followed-up for a median period of 8 years, together with age-matched women with normal breasts (normal control) and BC patients (cancer control), at the ratio of 1:2:2. Twenty-one breast cancers developed, 7 in the cases, 4 in the normal controls, and 10 in the BC controls, showing the relative risk (RR) with 95% confidence intervals (CI) to be 3.5 (1.03–11.9) in the cases with respect to the normal controls. The RR of the cases is not lower than that of contralateral breast cancer incidence. There were no significant differences in the risks of cancers in other organs among the groups. Pathological examination revealed that only atypical hyperplasia increased the RR of BC, as compared with the normal control breast group, or with non-proliferative disease. These results suggest that in a low-risk country, Japan, BBD is a definite risk factor for BC development as in high-risk countries.

Key words: Benign breast disease — Breast cancer risk — Retrospective cohort study — Atypical hyperplasia

In 1973, reviewing the etiology of human BC,[4] MacMahon et al.[1] gave the following two most probable explanations of the mechanism of the association between cystic mastitis and cancer: 1) the cystic disease itself is a premalignant condition that either predisposes to neoplastic change or is an early manifestation of malignant change, or 2) benign and malignant breast diseases have etiological factors in common — perhaps a particular hormonal pattern.

Since then many reports have been published in western countries supporting the hypothesis that women who have undergone a breast biopsy for BBD have an increased risk of BC.[2-13] The histological patterns, however, in the biopsied specimens have a broad histological spectrum from an almost normal condition to those which mimic *in situ* carcinoma.[14, 15] Furthermore, the compositions of the BBD components may be different among the studies depending on surgeons' and patients' attitudes to the necessity of breast biopsy. Regardless of these discrepancies in the BBD histology and patients' background characteristics, it has been quite well established that BBD, particularly some pathological entities with epithelial atypia, is one of the important risk factors for future BC development.[16, 17]

In order to elucidate the relationship between BBD and BC in Japan, where the incidence of BC is among the lowest in the world,[18] but has been rapidly increasing recently,[19] we performed a hospital-based retrospective cohort study, in which biopsied BBD patients were followed up for a median period of approximately 8 years, and subsequent BC incidence was compared with that in age-matched women with presumably normal breasts, and that in operated BC patients (metachronous contralateral BC).

PATIENTS AND METHODS

A total of 21, 430 patients visited the outpatient clinic of the National Kyushu Cancer Center from April, 1972 to the end of 1987. Of these, 455 were biopsied because of suspected cancer or large benign tumor(s), and were histologically confirmed to be benign. We excluded 2 male patients and 25 patients who were less than 30 years of age at the first visit to hospital, or who had BC or other cancers at or before the diagnosis of BBD. After all exclusions, 428 patients were evaluated as BBD.

Two kinds of control women were randomly selected from the above-mentioned out-patient clinic population. One was selected from women who visited our outpatient clinic for BC screening and who were considered normal on the basis of physical examinations and mammography at the time of their first visit. Patients with nodular or granular breasts, as well as any kind of tumor or inflammation were excluded from the "normal" breast group. Also, patients with tumorous or nodular mammograms were excluded from this group. The age was matched with the case to plus or minus 2 years, and also the date of the first visit to the hospital was the same within plus or minus 3 months of that of the case.

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[4] Abbreviations: BC, breast cancer; BBD, benign breast disease; AH, atypical hyperplasia; PDWA, epithelial proliferation without atypia; NON-PD, non-proliferative disease; RR, relative risk; CI, confidence interval.

A second control group, the BC control group, had the same entry criteria as the normal controls, except that the cancer control group was matched by the date of operation.

The number of patients entered in the control groups was 856 in each group, at the ratio of 1:2:2 to the cases. Mean age of the total patients (2,140) was 46.0 ± 0.3 (mean $\pm$ SE). We followed up the case and control patients for a median period of 99 months (mean; 105.5 ± 1.1) with a range of 3 to 18 years. Communication with the patients was mainly by telephone call or letter. Except for 169 patients who died during the folow-up period, 99% of the living women responded to the questions concerning the present status of their breasts and the development of cancers in breast or other organs. Background characteristics of these 3 groups were evaluated by means of specially designed questionaires at the time of the first visit to the outpatient clinic.

We divided the cases with biopsied BBD histologically into 3 categories by epithelial proliferation and/or atypia according to the classification of Black and Chabon.[20-22] Slides were reviewed by a pathologist (Y.K.). In these 3 subgroups, subsequent incidences of BC were compared.

Statistical difference in the background was analyzed by using the chi-square method. Calculation of the CI for RR was based on Morris and Gardner.[23]

RESULTS

The mean ages of the case and control groups were the same because of the matching of age (mean age with SE: 45.9 ± 0.5 years old in the cases, 45.7 ± 0.3 in the nomal controls, and 46.5 ± 0.3 in the cancer controls). Reproductive as well as non-reproductive background factors of the case and control patients were analyzed on the questionaires at the time of the first visit (Table I). Significant differences were noted among the three groups in some reproductive factors. There was a clear similarity in these characteristics between women in the case group and those in the cancer control group, but not between women in the case group and those in the normal control group.

The mean and the median follow-up periods were similar among the groups (median follow-up months: 100, 104, and 90 in the case, the normal control and the cancer control groups, respectively). The shorter period of the last group was due to earlier cancer death of the patients. During the follow-up period, we found 21 breast cancers (all invasive ductal cancer); 7 in the cases, 4 in the normal controls, and 10 in the cancer controls, i.e., 1.6%, 0.5%, and 1.1%, respectively.

In the BBD group, BC developed between 26 and 140 months (median 84, mean $\pm$ SD, 84 ± 42) after breast biopsy, in the ipsilateral breast in all but 1 case. The

period from the first diagnosis of "normal" breast to BC in the normal control group ranged between 76 and 115 months (median; 105 months, mean; 100 ± 18 months). In the cancer control group, contralateral BC developed 6 to 143 months after primary cancer operation (median; 60 months, mean; 65 ± 48 months). There are no statistically significant differances among the 3 groups in the period of cancer development.

Table II shows the RRs with 95% CI. The RR of the BBD group was 3.5, with 95% CI of 1.03 to 11.89 compared with the normal control group. The RR of contralateral BC development was shown to be 2.5 with the minimum 95% CI lower than 1.0, relative to the normal controls. When the development of BC in the BBD patients was compared with that of contralateral BC in the primary BC patients, a higher but non-significant RR was obtained (1.4, with 95% CI: 0.54–3.65), suggesting that the risk of developing BC in BBD patients is not lower than the metachronous contralateral BC incidence.

The effects of age on the risk of BC in these groups were studied. In the BBD patients who were less than 50 years old at the time of first diagnosis, 6 BC developed in 305 patients, and 1 in 123 patients at 50 years or more of age. Four cancers developed among 608 women less than 50 years old, with none in 248 who were 50 or more in the normal control. Five contrateral BCs developed out of 593 in the younger group, and 5 out of 263 in the older BC patients. There are no statistically significant differences among the age groups in the risk of BC development, partly because of the small numbers of positive events in the individual groups.

Subsequent development of cancers in other organs was also followed up. There are no significant differences among these 3 groups in the incidence of cancers in other organs with RR values in case and cancer control groups of 1.3 (95%CI: 0.55–3.23), and 1.4 (95%CI: 0.68–3.0), as compared with the normal breast group, respectively (Table III). In addition, no significant differences were noted in the distribution of organs involved among the groups (Table IV).

The patients with biopsied BBD was divided into 3 categories according to the presence or absence of epithelial proliferation and/or atypia according to the classification of Black and Chabon.[20-22] AH and/or PDWA were noted predominantly in mastopathy and intraductal or intracystic papilloma patients (Table V). Out of 428 BBD patients, there were 285 or 66.6% of patients with NON-PD, 109 (25.5%) of them with PDWA, and 34 (7.9%) AH patients. Out of 7 BBD patients who developed BC in the case group, 1, 2, and 4 patients were noted to belong to the NON-PD, PDWA, and AH groups, respectively (Table VI). A typical case of AH and the subsequently developed BC is shown in Fig. 1. When compared with the normal control, RR values of

Table I. Background Characteristics of Patients with Benign Breast Disease (Case) and Two Control Groups

Factor	Case (%)	Control 1 (%) (normal)	Control 2 (%) (cancer)	Total	P-value
No. of patients	428	856	856	2140	
Age					
30–39	110 (25.7)	221 (25.8)	200 (23.4)	531 (24.8)	
40–49	195 (45.6)	387 (45.2)	393 (45.9)	975 (45.6)	
50–59	86 (20.1)	175 (20.4)	187 (21.8)	448 (21.0)	$\chi^2=3.62$
60–69	26 (6.1)	56 (6.5)	51 (6.0)	133 (6.2)	$P=0.89$
70–	11 (2.6)	17 (2.0)	25 (2.9)	53 (2.5)	
Age at menarche					
–12	53 (12.4)	97 (11.3)	91 (10.6)	241 (11.3)	
13–15	275 (64.3)	545 (63.7)	576 (67.3)	1396 (65.2)	$\chi^2=3.59$
16–	99 (23.1)	209 (24.4)	182 (21.3)	490 (22.9)	$P=0.47$
Unknown	1	5	7	13 (6.1)	
Age at marriage					
Unmarried	45 (10.5)	25 (2.9)	75 (8.8)	145 (6.8)	
–21	97 (22.7)	185 (21.6)	173 (20.2)	455 (21.6)	
22–29	255 (59.6)	594 (69.4)	527 (61.6)	1376 (64.3)	$\chi^2=45.88$
30–	29 (6.8)	49 (5.7)	77 (9.0)	155 (7.2)	$P<0.001$
Unknown	2	3	4	9 (0.4)	
No. of pregnancies					
0	58 (13.6)	59 (6.9)	113 (13.2)	230 (10.7)	
1–3	170 (39.7)	303 (35.4)	358 (41.8)	831 (38.8)	$\chi^2=39.10$
4–	200 (46.7)	492 (57.5)	385 (45.0)	1077 (50.3)	$P<0.001$
Unknown	0	2	0	2 (0.1)	
Age at first childbirth					
0	82 (19.2)	90 (10.5)	163 (19.0)	335 (15.7)	
–22	68 (15.9)	122 (14.3)	118 (13.8)	308 (14.4)	
23–29	226 (52.8)	558 (65.2)	460 (53.7)	1244 (58.1)	$\chi^2=40.59$
30–	47 (11.0)	83 (9.7)	112 (13.1)	242 (11.3)	$P<0.001$
Unknown	5	3	3	11 (0.5)	
No. of live childbirths					
0	82 (19.2)	90 (10.5)	163 (19.0)	335 (15.7)	
1–2	244 (57.0)	527 (61.6)	479 (56.0)	1250 (58.4)	$\chi^2=28.82$
3–	102 (23.8)	238 (27.8)	213 (24.9)	553 (25.8)	$P<0.001$
Unknown	0	1	1	2 (0.1)	
History of BBD					
Yes	58 (13.6)	80 (9.3)	72 (8.4)	210 (9.8)	
No	367 (85.7)	760 (88.8)	784 (91.6)	1911 (89.3)	$\chi^2=8.95$
Unknown	3	16	0	19 (0.9)	$P=0.012$
Family history of breast cancer					
Yes	25 (5.8)	83 (10.3)	64 (7.5)	172 (8.0)	
No	402 (93.9)	765 (89.4)	791 (92.4)	1958 (91.5)	$\chi^2=6.59$
Unknown	1	8	1	10 (0.5)	$P=0.04$
Family history of other cancers					
Yes	191 (44.6)	406 (47.4)	375 (43.8)	972 (45.4)	
No	233 (54.4)	439 (51.3)	481 (56.2)	1153 (53.9)	$\chi^2=3.18$
Unknown	4	11	0	15 (0.5)	$P=0.21$
Height (cm)					
–149	93 (21.7)	161 (18.8)	211 (24.6)	465 (21.7)	
150–154	177 (41.4)	323 (37.7)	308 (36.0)	808 (37.8)	$\chi^2=36.41$
155–159	120 (28.0)	201 (23.5)	219 (25.6)	540 (25.2)	$P<0.001$
160–	38 (8.9)	171 (20.0)	118 (13.8)	327 (15.3)	
Unknown	0	0	0	0	
Body weight (kg)					
–49	159 (37.1)	274 (32.0)	313 (36.6)	746 (34.9)	
50–59	203 (47.4)	367 (42.9)	394 (46.0)	964 (45.0)	$\chi^2=1.31$
60–	65 (15.2)	129 (15.1)	149 (17.4)	343 (16.0)	$P=0.86$
Unknown	1	86	0	87 (4.1)	
Obesity (Quetlet index)					
–19.9	75 (17.5)	153 (17.9)	189 (22.1)	417 (19.5)	
20.0–22.9	209 (48.8)	322 (37.6)	354 (41.4)	885 (41.4)	$\chi^2=8.95$
23.0–24.9	78 (18.2)	149 (17.4)	157 (18.3)	384 (17.9)	$P=0.18$
25.0–	65 (15.2)	136 (15.9)	156 (18.2)	357 (16.7)	
Unknown	1	96 (11.2)	0	97 (4.5)	

Table II. Incidence of Breast Cancer in the Case and Two Control Groups and Relative Risks (RR)

Category	No. entered	No. of observed breast cancer	RR	95%CI
A. Case	428	7	3.5	1.03–11.89
Control 1 (normal)	856	4	1.0[a]	
Control 2 (cancer)	856	10	2.5	0.79–7.94
B. Case	428	7	1.4	0.54–3.65
Control 2 (cancer)	856	10	1.0[a]	

a) Reference group.

Table III. Observed Cancer in Other Organs in the Case and Control Groups and Relative Risks (RR)

Category	No. entered	No. of observed cancers in other organs	RR	95%CI
Case	428	8	1.33	0.55–3.23
Control 1 (normal)	856	12	1.0[a]	
Control 2 (cancer)	856	17	1.42	0.68–3.0

a) Reference group.

Table IV. Distribution of Observed Cancers in Other Organs

Category	No. entered	Observed cancer in other organs	Stomach	Cervical	Endo-metrial	Colon	Liver	Lung	Others
Case	428	8 (1.9%)	1	1	2	3	1	0	0
Control 1 (normal)	856	12 (1.4%)	2	0	0	3	2	2	3
Control 2 (cancer)	856	17 (2.0%)	5	4	1	2	1	0	4
Total	2140	37 (1.7%)	8	5	3	8	4	2	7

Table V. Clinical Diagnosis of Biopsied Benign Breast Disease (the Cases) and Histolocal Classification by Epithelial Proliferation and/or Atypia

Clinical diagnosis	NON-PD (%)	PDWA (%)	AH (%)	Total (%)
Mastopathy	172 (65.2)	67 (25.4)	25 (9.5)	264 (100)
Papilloma	0 (0)	19 (73.1)	7 (26.9)	26 (100)
Phyllodes tumor	7 (33.3)	13 (61.9)	1 (4.8)	21 (100)
Fibroadenoma	75 (89.3)	8 (9.5)	1 (1.2)	84 (100)
Inflammation	24 (96.0)	1 (4.0)	0 (0)	25 (100)
Others	7 (87.5)	1 (12.5)	0 (0)	8 (100)
Total	285 (66.6)	109 (25.5)	34 (7.9)	428 (100)

Abbreviations: NON-PD, non proliferative disease; PDWA, proliferative disease without atypia; AH, atypical hyperplasia.

Table VI. Developed Breast Cancers in the Cases

No.	Benign breast disease			DFI (mo)	Breast cancer		Developed in the same portion of the breast[a]
	Age at entry	Clinical diagnosis	Histological classification		Tumor size (cm)	Histological type	
1	38	fa	NON-PD	26	2.0+1.5	IDC	no
2	44	fa	PDWA	76	2.4	IDC	no
3	42	pap	PDWA	140	1.6	IDC	no
4	49	mp	AH	94	1.6	IDC	no
5	43	mp	AH	38	1.6	IDC	yes
6	36	mp	AH	84	1.6	IDC	yes
7	58	pap	AH	128	5.5	IDC	yes

Abbreviations: fa, fibroadenoma; pap, papilloma; mp, mastopathy; NON-PD, non-proliferative disease; PDWA, proliferative disease without atypia; AH, atypical hyperplasia; DFI, disease-free interval (months); IDC, invasive ductal cancer.
a) Breast tumor(s) was located in the vicinity of biopsied benign breast disease.
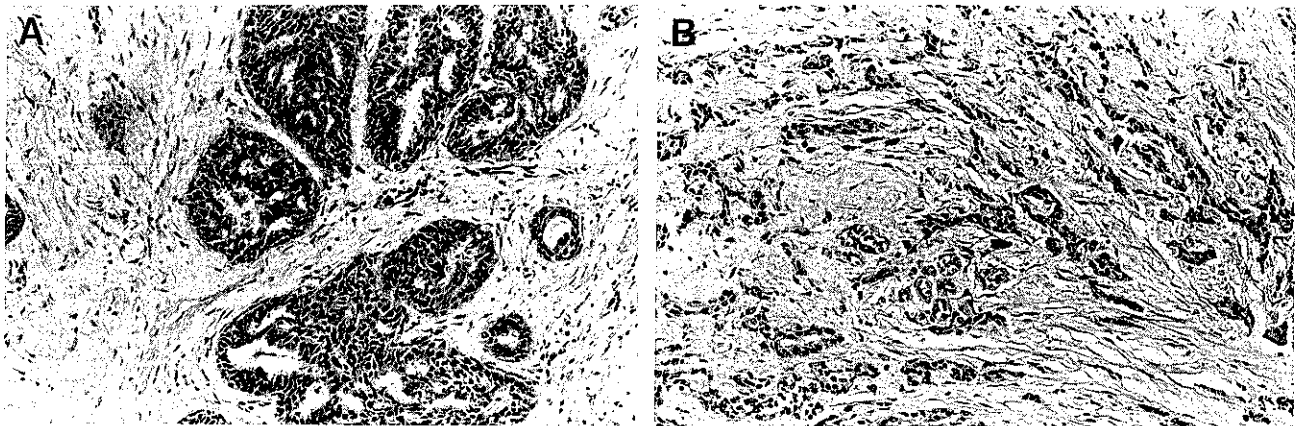
Fig. 1. A. histological picture of atypical ductal hyperplasia (case 4). Papillary, arcade-like, and solid proliferations of ductal epithelial cells are apparent in the lumina of ducts. Epithelial projections are present without evident stroma. Moderate nuclear pleomorphism and disturbance of polarity are noted. H & E, ×50. B. After 94 months, a small tumor developed in the breast region approximately 3 cm from the biopsy site. Small cancer cell nests showing infiltrative growth with a scirrhous pattern are scattered in the connective tissue. H & E ×50.

Table VII. Relative Risks of Patients with Benign Breast Diseases for Breast Cancer according to Epithelial Proliferation and/or Atypia

Category	No. entered	Cancer observed	RR	95%CI
A. NON-PD	285	1	0.75	0.08–6.68
PDWA	109	2	4.0	0.34–9.85
AH	34	4	25.2	3.68–172.78
Control 1 (normal)	856	4	1.0[a]	
B. PDWA	109	2	5.3	0.49–58.20
AH	34	4	33.4	3.85–290.3
NON-PD	285	1	1.0[a]	
C. AH	34	4	6.4	1.22–33.45
PDWA	109	2	1.0[a]	

a) Reference group.

NON-PD, PDWA, and AH were 0.75, 4.0, and 25.2, respectively (Table VII). The 95% CI of RR for AH ranged from 3.7 to 173, suggesting the existence of a significant difference. On the basis of NON-PD, RR values of PDWA and AH groups are 5.3 and 33.4, respectively, and again BBD patients with AH histology alone clearly showed a significantly higher RR compared to those with NON-PD. Table VII also indicates that as compared with PDWA, the future BC risk of AH patients was significantly higher, with RR of 6.4 (95%CI: 1.22–33.45).

Patients' reproductive and non-reproductive characteristics in these 3 subgroups were studied. There were no significant differences among the groups. Thus, it may be difficult on the basis of reproductive characteristics alone to identify the AH patients who may most frequently develop BC later. The relationship of epithelial proliferation and/or atypia on the BBD group and the subsequent BC to the family history of BC was studied. Only 5.6% or 24 out of 428 of BBD patients had a family history of BC, among which 5 patients had BCs in mother or sisters. In only 1 of 7 patients who developed BC subsequently was a family history of BC noted.

DISCUSSION

A retrospective cohort study concerning the BC risk subsequent to BBD was conducted in a hospital-based case-control group. In this study, two kinds of control groups were included; age-matched women with normal breasts, and BC patients operated in the same hospital at the same period.

In the follow-up study of BBD as a BC risk, 3 types of control group have been used; the general population[2-5, 10, 13, 20] or women with normal breasts in a large screening project,[9, 11, 12] or a hospital-based control as in this study,[8] or an internal comparison group in the case of pathological selection.[6, 22] Even after excluding women with a history of breast biopsy, the general population has a substantial proportion of BBD, clinically up to 50%,[24] and this may contaminate the "normal" breast group with various proportions of BBD, causing an underestimation of BC risk in a BBD study.[8, 25]

On the contrary, in a hospital-based study such as this, although case-control studies are able to be performed even if cancer registry data are incomplete, the "normal" control women have a bias in that even in the case of screening of cancer, they visit the hospital because of

being more conscious of their breasts. In this group, there may be more BBD patients than in the general population. In this study, however, the "normal" control group was strictly evaluated by means of physical examinations and mammography, and only women concluded not to have any pathological findings in the breasts were included in the normal control group.

The RR of BC development in women with BBD was shown to be significantly higher than in those with normal breasts, with an RR estimate of 3.5 with 95%CI of 1.03–11.89 (Table II). According to Webber and Boyd,[8] among 36 cohort studies assessed, RR varied widely from 1.2 to 18.0, and 22 studies claimed to find an association with BC risk. Most of the subsequently performed studies confirmed the results by exhibiting increased cancer risks overall or in some subgroups of BBD.[6, 9–13] The results in this study confirmed the elevated BC risk of BBD women in a low-risk country (Japan), as in high-risk[6, 9, 12, 13] and moderate-risk countries.[10, 11] By including a second control, i.e., BC patients, we compared the subsequent BC risk in the BBD group with the so-called metachronous contralateral BC risk. As shown in Table II, there was no significant difference in the risks between the two groups. The risk of developing cancer in the second breast was reported to be five times,[26] 2.9 times[27] or 2.4 times[28] greater than the normal risk of initial BC in the general population. In this study, RR of contralateral BC was noted to be 2.5 with 95% CI of 0.79–7.94. showing a marked but non-significant difference from the development of the first primary cancer in women with normal breasts. Furthermore, the risk of developing primary BC in the BBD group was not lower than the metachronous contralateral BC risk in the primary BC patients (Table II).

We studied whether or not the elevated BC risk in BBD patients is dependent on general promotion of carcinogenesis processes in the whole body. As indicated in Tables III and IV, among the 3 groups, there were no significant differences in the observed cancer risks in other organs than breasts, or in the distribution of involved sites, suggesting that the stimulated carcinogenic process, if it exists, appears to be resticted to the mammary parenchyma.

Pathological examinations revealed that 7.9, 25.5, and 66.6% of 428 BBD patients, respectively, showed AH, PDWA and NON-PD, according to the classification of Black and Chabon.[20–22] Table VII shows that NON-PD, the most frequently observed histological subgroup of BBD, had a similar cancer risk to the normal control. There was a small increase in the cancer risk in patients with PDWA as compared with the normal control or women with NON-PD breasts, but the differences were not significant. It has been reported that women with PDWA are at slightly increased risk of BC, with RR

generally less than 2.0.[6, 9, 11–13] The results in this study are similar, if somewhat higher, indicating no significant increase in risk.

On the contrary, the risk in women with AH was 25.2 times that in women with normal breasts, or 33.4 times greater than that in women with NON-PD breasts, or 6.4 times greater than that in those with PDWA. The wide ranges of 95% CI were because of the small numbers of developed cancers. As shown in Table VI, 3 of 4 patients with AH developed BC in the vicinity of the biopsied portion of the breast, while BBD patients with other components had cancer at a site unrelated to the biopsied portion. These findings suggest a close relationship between AH and BC. However, a relatively long period appears to be necessary for the development of the future BC.

These results support the findings that, among women with biopsy-confirmed BBD, a certain histological type confined to atypical epithelial hyperplasia is at significantly elevated risk for development of BC.[2–6, 9, 11–13, 16, 19, 22] The wide range of the proportion of AH in BBD, 2.0%,[2] 2.2%,[11] 3.6%,[6] 5.4%,[3] 6.9%,[13] 7.8%,[9] 7.9% (this study), or 12.2%,[12] suggests that along with different distributions in the characteristics of the BBD patients who received breast biopsy, there is a possibility of discrepancy in the classification of AH among the studies.

There have been various efforts to specify more precisely the higher risk group in the AH patients, on the basis of family history,[6, 9, 22] calcification,[6, 9] menopausal status,[12] and age at first birth.[29] We studied the distribution of reproductive and non-reproductive characteristics of women who were subclassified histologically into 3 groups (data not shown). No significant differences in the distributions of the factors studied were found among the 3 groups. Thus, it may be difficult by means of these background factors alone to identify or to specify more precisely the subgroups of AH patients who may later develop BC.

As there is some controversy concerning the criteria of AH, and its significance in breast diseases is not fully accepted, particularly in Japan, more accurate and refined methods to predict the subgroup of BBD patients who will develop BC in later years are needed. Until then, the histological examination of proliferation and atypia in BBD may be a useful tool in this field.

In conclusion, these results suggest that in Japan, where the incidence of BC is among the lowest in the world, as in high-risk and moderate-risk countries, BBD is one of the significant risk factors for BC. Special consideration should be given to the management of the histologically classified subgroup of BBD patients with higher risk; more frequent follow-up for a longer period may be desirable.

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