Jpn. J. Cancer Res. **90**, 600–606, June 1999

Risk of Breast Cancer in Japanese Women with Benign Breast Disease

Yuko Minami,[1, 2, 7] Noriaki Ohuchi,[3] Yoshinori Taeda,[4] Akira Takano,[5] Akira Fukao,[6] Susumu Satomi[3] and Shigeru Hisamichi[2]

[1]Division of Epidemiology, Miyagi Cancer Center Research Institute, 47-1 Nodayama, Medeshima-Shiode, Natori 981-1293, [2]Department of Public Health, Tohoku University School of Medicine, 2-1 Seiryomachi, Aoba-ku, Sendai 980-8575, [3]Second Department of Surgery, [4]First Department of Pathology, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8575, [5]Miyagi Prefectural Cancer Registry, c/o Miyagi Cancer Society, 6-2-81 Kamisugi, Aoba-ku, Sendai 980-0011 and [6]Department of Public Health, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-2331

To investigate the risk of breast cancer development in women with benign breast disease (BBD), 387 screen-detected BBD women and 1,489 normal women, taken from participants in the breast cancer screening program during 1978–1986, were followed through 1991. While 2,811 person-years in the BBD group and 11,018 person-years in the normal group were accumulated, 5 women in the BBD group and 6 women in the normal group developed breast cancer. Using the Mantel-Haenszel method, relative risks (RR) were estimated for all women with BBD and women in some BBD types. Significantly elevated risk of breast cancer was observed in all women with BBD (RR=3.26, 95% confidence interval (CI) 1.08–9.83). Women with proliferative BBD were at high risk of breast cancer (RR=8.48, 95%CI 2.99–24.10), but no increased risk was observed for women with non-proliferative BBD (RR=0.93, 95%CI 0.11–7.66). These results are consistent with those in high-risk countries for breast cancer. In the management of women with BBD, histopathological diagnosis of the breast lesion is essential and women with proliferative BBD should be followed up carefully.

Key words: Benign breast disease — Breast cancer risk — Cancer registry — Retrospective cohort study — Screening

It has been reported that a history of benign breast disease (BBD) increases breast cancer risk,[1–4] but recent studies have shown that the risks for subsequent breast cancer in BBD patients who have had a biopsy are different among different histopathological types.[5–19] While the histopathological classification systems used in these studies were not the same, there was a consistent finding that atypical hyperplasia (AH) presents high risk for the development of breast cancer.[20] Although Japan is one of the countries with low risk for breast cancer, the incidence rate of female breast cancer is gradually increasing.[21] A number of epidemiological studies of breast cancer have recently been conducted and the characteristics of Japanese women with breast cancer have been clarified.[3,4,22–25] However, there have been few studies on the prognosis in BBD patients[18] and the relation of BBD to breast cancer risk is unclear in Japan.

We have reported similarities of background characteristics between proliferative BBD (including AH) and breast cancer, using data obtained from breast cancer screening participants.[26] The present study was conducted in order to evaluate the subsequent breast cancer risk among the BBD patients described in the previous report. Accumulations and comparisons of data among countries with different risk for breast cancer seem necessary for elucidating the association of BBD lesions with breast cancer risk. This study provides additional data from a low-risk country for breast cancer.

MATERIALS AND METHODS

Study subjects and histopathological classification This study was conducted by using data obtained from breast cancer screening participants during 1978–1986. The breast cancer screening was based on clinical breast examination, i.e., inspection and palpation of the breasts and the axillar lymph nodes. The methods of data collection have been described in a previous report.[26] Briefly, during the screening period, a total of 678 women had undergone surgical biopsy at community referral hospitals and 571 biopsies were diagnosed as benign. These benign subjects were candidates for study subjects. Since 34 biopsies were derived from double biopsies for 17 women, only the first biopsy was taken as the study subject. Consequently, 554 women were selected. In 1991, the collection of their slides from hospitals was attempted for review. Among the

[7] To whom correspondence should be addressed at the Division of Epidemiology, Miyagi Cancer Center Research Institute.
E-mail: adym@mcc.pref.miyagi.jp

biopsy specimens 164 slides for 164 women were missing, and 390 slides for 390 women were available to be assessed. For each BBD subject, 4 subjects 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 screening. Only one normal subject each for 8 BBD subjects, 2 normal subjects each for 5 BBD subjects and 3 normal subjects each for 5 BBD subjects were found eligible. No eligible normal subjects were found for 5 BBD subjects. In total 1,501 matched normal subjects were selected.

Three hundred and ninety slides with the first BBD diagnosis were reviewed and reclassified by two of the authors (Y. T. and N. O.) according to the classification of Dupont and Page,[27–29] i.e., fibrocystic change (FCC), proliferative disease without atypia (PDWA), AH and ductal carcinoma *in situ* (DCIS). Three slides were diagnosed as DCIS and were excluded from subsequent investigation. Finally, 387 BBD subjects including 5 BBD subjects with no eligible matched normal subjects, and 1,489 normal subjects were available for this study. The BBD subjects were regrouped into two major categories according to the presence of epithelial proliferation, i.e., (1) proliferative disease (PD) including PDWA and AH and (2) non-proliferative disease (Non-PD) including FCC, fibroadenoma, lipoma and panniculitis.

Follow-up of study subjects Follow-up to determine prognosis (survival, mortality, moved away and cancer incidence) began in the year of biopsy (the year of entry into the study) and ended in 1991. The mortality and moved away classifications were based on examinee files in the regional cancer screening center and resident registration files in the local government office of each municipality. The women listed in the examinee file in 1991 were treated as having survived. To investigate cancer incidence, a computer file of study subjects was linked to the file of the Miyagi Prefectural Cancer Registry, Sendai, Japan. As for breast cancer, only "invasive cancer" was counted as incidence. In order to examine the effect of detection bias on breast cancer risk, screening histories for breast cancer during the follow-up period were extracted from the file of each subject in the screening center.

Statistical analysis In the analysis, we ignored the matched design because the unmatched analysis enabled the inclusion of BBD subjects for whom no eligible matched normal subjects had been found. Namely, in each analysis, BBD subjects were compared with 1,489 normal subjects. Person-years from the date of entry into the study to the date of diagnosis of cancer, the date of death, the date of having moved away, or the date of terminating the study, were calculated for each subject. The count of cancer incidence started at 12 months after the date when the follow-up began. Analyses were carried out for two major categories, PD and Non-PD, respectively. The risk of breast cancer adjusted for age (–39, 40–49, 50–59, 60–) and place of screening (urban, rural) was estimated using the Mantel-Haenszel method.[30] In addition, the risks for cancers of other sites were also investigated.

To evaluate the effect of detection bias, screening histories for breast cancer were compared between BBD subjects and normal subjects by analysis of variance using the LSMEANS option of the GLM Procedure in the SAS program.[31,32] In this model, the adjusted means of screening participation frequency during the follow-up period were calculated, taking into account the year of entry, age at entry and place of screening.

RESULTS

Table I shows the status of study subjects at the end of the study. Follow-up was completed for 371 BBD subjects and 1,444 normal subjects (survived and free of cancer in 1991, deceased or developed cancer) and 2 BBD subjects and 9 normal subjects were partially followed (moved away). Fourteen BBD subjects and 36 normal subjects

Table I. Prognosis of BBD Subjects and Normal Subjects during the Follow-up Period

Histopathological type (No.)	Survived	Deceased	Moved away	Developed cancer[a)]	Lost to follow-up
Normal (1,489)	1,402	5	9	37	36
BBD (387)	355	1	2	15	14
AH (17)	14	0	0	2	1
PDWA (114)	98	0	1	8	7
Non-PD (256)	243	1	1	5	6

a) Death from cancer is included.
BBD, benign breast disease; AH, atypical hyperplasia; PDWA, proliferative disease without atypia; Non-PD, non-proliferative disease.

were not traced (lost to follow-up). The average duration of follow-up for the 1,826 subjects was 7.6 years, and 2,811 person-years in the BBD group and 11,018 person-years in the normal group were accumulated. In the followed-up subjects, the mean age at entry for PD subjects was 44.1 years, that for Non-PD subjects was 45.8 years and that for normal subjects was 45.4 years.

Table II shows the risk of breast cancer among BBD subjects as compared with normal subjects. Five subjects (one subject with AH, 3 subjects with PDWA and one subject with FCC) in the BBD group and 6 subjects in the normal group developed breast cancer. Women with BBD had a significantly higher risk of breast cancer as a whole (relative risk (RR)=3.26; 95% confidence interval (CI) 1.08–9.83). The risk of breast cancer according to histopathological classification was 8.48 for PD and 0.93 for Non-PD. No increased risk was observed for women with Non-PD. The risk of breast cancer in women with AH was estimated to be extremely high, but the 95%CI was wide due to small sample size. In summary, with increasing degree of proliferation and abnormality in the epithelium, the risk of breast cancer tended to increase. The profiles of the subjects who developed breast cancer are shown in Table III. Of 5 subjects in the BBD group, two had been diagnosed as having cancer within two years after biopsy and the other three, between 7 and 10 years after biopsy. Six subjects in the normal group had been diagnosed within 6 years. Furthermore, two subjects in the BBD

Table II. Relative Risks of Breast Cancer in Relation to Histopathological Type of Benign Breast Disease

Histopathological type	Person-years	Incidence	Relative risk[a)]	95% confidence interval
Normal	11,018	6	1.00	
BBD (Total)	2,811	5	3.26	1.08–9.83[b)]
PD	888	4	8.48	2.99–24.10[b)]
AH	102	1	16.03	3.34–76.87[b)]
PDWA	786	3	7.26	2.17–24.26[b)]
Non-PD	1,923	1	0.93	0.11–7.66

a) Relative risk was adjusted for age and place of screening.
b) Statistically significant at $P<0.05$.
BBD, benign breast disease; PD, proliferative disease; AH, atypical hyperplasia; PDWA, proliferative disease without atypia; Non-PD, non-proliferative disease.

Table III. Profiles of Subjects Developing Breast Cancer in the BBD Group and Normal Group

No.	Age at entry (years)	Histopathological type	Disease-free interval (months)	Place of diagnosis of cancer	Age at menarche (years)	Parity number	Breast feeding for the last child
BBD							
1	63	AH	85	Clinic	14	2	Insufficient, 13 mo[a)]≤
2	40	PDWA	102	Clinic	13	2	Never
3	49	PDWA	21	Screening	15	2	Insufficient, 13 mo≤
4	53	PDWA	14	Screening	13	0	—
5	49	FCC	115	Clinic	14	3	Sufficient, 7–12 mo
Normal							
1	35	Normal	39	Clinic	13	2	Sufficient, 6 mo≥
2	39	Normal	47	Clinic	12	1	Sufficient, 13 mo≤
3	42	Normal	30	Screening	14	2	Never
4	45	Normal	66	Clinic	14	0	—
5	46	Normal	19	Clinic	13	2	Never
6	48	Normal	58	Clinic	16	2	Sufficient, 13 mo≤

a) mo, months.
AH, atypical hyperplasia; PDWA, proliferative disease without atypia; FCC, fibrocystic change.

Table IV. Relative Risks for Cancers of Other Sites Associated with Benign Breast Disease

Histopathological type	Person-years	Incidence	Relative risk[a)]	95% confidence interval
All sites excluding breast cancer				
Normal	11,018	31	1.00	
BBD	2,811	10	1.29	0.64–2.63
Stomach cancer				
Normal	11,018	5	1.00	
BBD	2,811	1	0.80	0.10–6.83
Colon cancer				
Normal	11,018	3	1.00	
BBD	2,811	2	2.50	0.45–13.72
Thyroid cancer				
Normal	11,018	5	1.00	
BBD	2,811	3	2.45	0.61–9.84

a) Relative risk was adjusted for age and place of screening.
BBD, benign breast disease.

Table V. Adjusted Means of Breast Cancer Screening Participation Frequency during the Follow-up Period

	Model	Adjusted mean[a)]	95% confidence interval	*P* value for *F* statistics
I.	BBD (total)	3.63	3.36–3.90	
	Normal	3.18	3.00–3.36	0.0005
II.	PD	3.58	3.16–4.01	
	Normal	3.24	3.05–3.43	0.0963
III.	Non-PD	3.69	3.38–4.00	
	Normal	3.19	3.01–3.38	0.0011

a) Adjusted mean was estimated by taking into account the year of entry into the study, age at entry and place of screening.
BBD, benign breast disease; PD, proliferative disease; Non-PD, non-proliferative disease.

group and one subject in the normal group were detected by screening. No subject with a family history of breast cancer in mother or sisters developed breast cancer. One subject each in the BBD group and normal group was nulliparous.

The risks for cancers of other sites are presented in Table IV. For all sites excluding breast cancer and stomach cancer, the risks in women with BBD were unity. The risks of cancers of the colon and thyroid were elevated in women with BBD, but the increases were not significant.

Table V shows the adjusted means of breast cancer screening participation frequency in BBD subjects and normal subjects. The mean of frequency in 373 BBD subjects was significantly larger than that in 1,453 normal subjects. The means of frequency in PD subjects and Non-PD subjects were also larger than those of normal subjects. However, the difference in the means of frequency between BBD subjects and normal subjects was less than 0.5 for either of the histopathological groups and the 95%CI in PD overlapped between BBD subjects and normal subjects.

DISCUSSION

We conducted a retrospective cohort study of participants in the breast cancer screening program, and estimated the risks of cancers of the breast and other sites associated with BBD. Women with BBD were at significantly increased risk of breast cancer. The magnitude of breast cancer risk varied according to histopathological type. We compared this result with other data reported previously from Western countries and Japan.[5–19)] The finding that PD lesion carries a higher risk of breast cancer than Non-PD lesion is consistent with these results. However, while the risk estimate associated with AH in Western countries has ranged from 3.0 to 13.0,[5, 6, 8–12, 14–17, 19)] that in Japan (including our data) is extremely large, ranging from 16.0 to 30.0.[18)] One possible explanation for the difference is that the sample size of the Japanese studies was smaller than those of Western studies. The number of BBD subjects in our study was 390 (inclusive of DCIS), and that in Nomura's study in 1993 was 428.[18)] Even if we completely followed all BBD subjects, the number of subjects would be 554 at most. The previous pathological study also revealed a difference in frequency of epithelial hyperplasia between Japanese women in Hawaii and Japan; the frequency in second-generation Japanese-Hawaiian (nisei) women was much larger than that in Japanese.[33)] Thus, it

seems inevitable that the sample size in Japanese studies was much smaller than that in Western studies. To get a stable risk estimate with a narrow range of confidence interval, longer-term follow-up is necessary.

There is a possibility that differences of classification system might influence the magnitude of breast cancer risk in AH. Most of the recent studies have used either Black-Chabon or Dupont-Page criteria. Whichever criteria had been used, the risk of breast cancer associated with AH was found to significantly increase. But in the Black-Chabon criteria, atypia grades 3 and 4 are considered as AH,[5,34] whereas the Dupont-Page criteria recognize AH only in atypia grade 4 of the Black-Chabon criteria.[9] Consequently, some of the AH lesions according to the Black-Chabon criteria would be classified as PDWA according to the Dupont-Page criteria.[9] Actually, the frequency of AH lesion varied among the studies. Among the Japanese studies, the frequency of AH lesions in Nomura's study using Black-Chabon criteria was 7.9%,[18] whereas that in our study using Dupont-Page criteria was 4.4%. Concerning the biological characteristics of AH, there is some evidence indicating that AH based on Dupont-Page criteria has a higher risk for breast cancer.[20] One of the authors (N.O.) has already reported that expression of cytoplasmic DF3 antigen in AH was similar to that in DCIS.[35]

The major problems in this study seem to be loss to follow-up and the possibility of detection bias. Concerning the problem of loss to follow-up, we investigated the quality of follow-up methods and its influence on the present results. The prognosis was investigated mainly based on examinee files of the regional cancer screening center and resident registration files, which data have high reliability. Miyagi Prefectural Cancer Registry, used for measuring cancer incidence, also has a high quality of data collection.[36] As for the registry data during 1978–1992, the percentage of breast cancer cases registered from death certificates only was 1.5 and that of breast cancer cases verified histopathologically was 94.5.

In the present study, 1,826 subjects among 1,876 original study subjects were followed and the follow-up rate (97.3%) was regarded as sufficiently high. No breast cancer occurrence among loss to follow-up subjects (14 BBD subjects and 36 normal subjects) was detected in cancer registry files. Accordingly, it is unlikely that loss to follow-up substantially distorted the results. However, at the stage of identification of the study population, 164 women with the diagnosis of BBD, whose slides were missing, were excluded. There is a possibility that the excluded subjects might influence the true risk of breast cancer associated with BBD. We linked the list of 164 excluded subjects with cancer registry files and calculated cumulative cancer incidence rate during 1979–1991, ignoring their prognosis. In the excluded subjects, the cumulative incidence rate of all sites was 4.88% and that of breast cancer was 1.22%. These rates were similar to those in 390 BBD subjects inclusive of DCIS. Furthermore, the mean age of the excluded women (45.2 years) was similar to that of the 390 BBD subjects (45.1 years). Taking these assessments into consideration, the characteristics of the excluded subjects are not likely to have influenced the present results.

To evaluate the possibility of detection bias, we compared the screening histories of breast cancer between BBD subjects and normal subjects. This comparison indicated that the difference in screening participation frequency between PD subjects and normal subjects was insignificant (Table V). Furthermore, we counted only invasive breast cancer as breast cancer incidence. It is unlikely that women with BBD might be earlier diagnosed as breast cancer. Therefore, the effect of detection bias on our findings was considered unlikely to be serious. However, there is a possibility that the insignificant difference between PD subjects and normal subjects might be due to the small sample size of the PD group, since the results in two other comparisons (models I and III in Table V) were significant. Although a significant difference between Non-PD subjects and normal subjects is not likely to alter the direction of breast cancer risk, the effect of detection bias on the risk estimate for PD might not be completely negligible.

We have already reported the similarity of background characteristics between proliferative BBD (AH and PDWA) and breast cancer. However, to investigate further the association between BBD and breast cancer, clarification of the profiles of BBD subjects who subsequently developed breast cancer is needed.[11] The profiles among the subjects developing breast cancer are shown in Table III. A more detailed analysis of the current data indicated that PD subjects developing breast cancer tended to have earlier menarche than PD subjects not developing breast cancer. The mean age at diagnosis of breast cancer in the PD group (56 years) was larger than that in the normal group (46 years). It seems that most breast cancer subjects in the PD group might be menopausal at diagnosis of breast cancer. These observations are consistent with the general characteristics of breast cancer. In particular, the late age at diagnosis of breast cancer in the PD group is comparable with our previous finding; BBD is a risk factor for late onset breast cancer. In the previous report, we also suggested that breast function might be a determinant of prognosis (benign or malignant).[26] Cumulative incidence rate of breast cancer in PD subjects with insufficient (never or insufficient) milk production was 6.4%, and there was no occurrence of breast cancer in PD subjects with sufficient milk production (data not shown in the table). This finding seems to support our suggestion.

In conclusion, although this study is small-scale, the results are consistent with those in high-risk countries for

breast cancer, i.e., women with proliferation and atypia in breast epithelium were at increased risk of breast cancer. However, among the 387 BBD subjects, 33.9% were proliferative. The remainder, 66.1% were non-proliferative, and were not at increased risk of breast cancer. Namely, frequent follow-up examination is not necessary for a majority of women with BBD, i.e., for women with Non-PD. In the management of women with BBD, histopathological diagnosis of the breast lesion is essential and women with AH or PDWA should be followed up carefully.

ACKNOWLEDGMENTS

This study was supported in part by the Kurokawa Cancer Foundation, Sendai. We are grateful to the Advisory Committee of Breast Cancer Screening, Miyagi Cancer Society. We are also grateful to the staff at all the municipalities that participated in this study and to Dr. M. Sato for helpful information on follow-up survey.

(Received February 3, 1999/Revised March 18, 1999/Accepted March 24, 1999)

REFERENCES

1) Brinton, L. A., Williams, R. R., Hoover, R. N., Stegens, N. L., Feinleib, M. and Fraumeni, J. F., Jr. Breast cancer risk factors among screening program participants. *J. Natl. Cancer Inst.*, **62**, 37–43 (1979).
2) Helmrich, S. P., Shapiro, S., Rosenberg, L., Kaufman, D. W., Slone, D., Bain, C., Miettinen, O. S., Stolley, P. D., Rosenshein, N. B., Knapp, R. C., Leavitt, T., Jr., Schottenfeld, D., Engle, R. L., Jr. and Levy, M. Risk factors for breast cancer. *Am. J. Epidemiol.*, **117**, 35–45 (1983).
3) Hirohata, T., Shigematsu, T., Nomura, A. M. Y., Nomura, Y., Horie, A. and Hirohata, I. Occurrence of breast cancer in relation to diet and reproductive history: a case-control study in Fukuoka, Japan. *Natl. Cancer Inst. Monogr.*, **69**, 187–190 (1985).
4) Minami, Y., Ohuchi, N., Fukao, A. and Hisamichi, S. Risk factors for breast cancer: a case-control study of screen-detected breast cancer in Miyagi Prefecture, Japan. *Breast Cancer Res. Treat.*, **44**, 225–233 (1997).
5) Black, M. M., Barclay, T. H. C., Cutler, S. J., Hankey, B. F. and Asire, A. J. Association of atypical characteristics of benign breast lesions with subsequent risk of breast cancer. *Cancer*, **29**, 338–343 (1972).
6) Kodlin, D., Winger, E. E., Morgenstern, N. L. and Chen, U. Chronic mastopathy and breast cancer: a follow-up study. *Cancer*, **39**, 2603–2607 (1977).
7) Roberts, M. M., Jones, V., Elton, R. A., Fortt, R. W., Williams, S. and Gravelle, I. H. Risk of breast cancer in women with history of benign disease of the breast. *Br. Med. J.*, **288**, 275–278 (1984).
8) Hutchinson, W. B., Thomas, D. B., Hamlin, W. B., Roth, G. J., Peterson, A. V. and Williams, B. Risk of breast cancer in women with benign breast disease. *J. Natl. Cancer Inst.*, **65**, 13–20 (1980).
9) Dupont, W. D. and Page, D. L. Risk factors for breast cancer in women with proliferative breast disease. *N. Engl. J. Med.*, **312**, 146–151 (1985).
10) Page, D. L., Dupont, W. D., Rogers, L. W. and Rados, M. S. Atypical hyperplastic lesions of the female breast: a long-term follow-up study. *Cancer*, **55**, 2698–2708 (1985).
11) Dupont, W. D. and Page, D. L. Breast cancer risk associated with proliferative disease, age at first birth, and a family history of breast cancer. *Am. J. Epidemiol.*, **125**, 769–779 (1987).
12) Carter, C. L., Corle, D. K., Micozzi, M. S., Schatzkin, A. and Taylor, P. R. A prospective study of the development of breast cancer in 16,692 women with benign breast disease. *Am. J. Epidemiol.*, **128**, 467–477 (1988).
13) Brinton, L. A. Relationship of benign breast disease to breast cancer. *Ann. N.Y. Acad. Sci.*, **586**, 266–271 (1990).
14) Palli, D., Rosselli Del Turco, M., Simoncini, R. and Bianchi, S. Benign breast disease and breast cancer: a case-control study in a cohort in Italy. *Int. J. Cancer*, **47**, 703–706 (1991).
15) London, S. J., Connolly, J. L., Schnitt, S. J. and Colditz, G. A. A prospective study of benign breast disease and the risk of breast cancer. *J. Am. Med. Assoc.*, **267**, 941–944 (1992).
16) McDivitt, R. W., Stevens, J. A., Lee, N. C., Wingo, P. A., Rubin, G. L., Gersell, D. and the Cancer and Steroid Hormone Study Group. Histologic types of benign breast disease and the risk for breast cancer. *Cancer*, **69**, 1408–1414 (1992).
17) Dupont, W. D., Parl, F. F., Hartmann, W. H., Brinton, L. A., Winfield, A. C., Worrell, J. A., Schuyler, P. A. and Plummer, W. D. Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. *Cancer*, **71**, 1258–1265 (1993).
18) Nomura, Y., Tashiro, H. and Katsuda, Y. Benign breast disease as a breast cancer risk in Japanese women. *Jpn. J. Cancer Res.*, **84**, 938–944 (1993).
19) Marshall, L. M., Hunter, D. J., Connolly, J. L., Schnitt, S. J., Byrne, C., London, S. J. and Colditz, G. A. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. *Cancer Epidemiol. Biomarkers Prev.*, **6**, 297–301 (1997).
20) Ma, L. and Boyd, N. F. Atypical hyperplasia and breast cancer risk: a critique. *Cancer Causes Control*, **3**, 517–525 (1992).
21) The Research Group for Population-Based Cancer Registration in Japan. Cancer incidence in Japan. *Gann Monogr. Cancer Res.*, **41**, 107–158 (1994).
22) Kato, I., Miura, S., Kasumi, F., Iwase, T., Tashiro, H., Fujita, Y., Koyama, H., Ikeda, T., Fujiwara, K., Saotome,

K., Asaishi, K., Abe, R., Nihei, M., Ishida, T., Yokoe, T., Yamamoto, H. and Murata, M. A case-control study of breast cancer among Japanese women: with special reference to family history and reproductive and dietary factors. *Breast Cancer Res. Treat.*, **24**, 51–59 (1992).
23) Yoo, K.-Y., Tajima, K., Kuroishi, T., Hirose, K., Yoshida, M., Miura, S. and Murai, H. Independent protective effect of lactation against breast cancer: a case-control study in Japan. *Am. J. Epidemiol.*, **135**, 726–733 (1992).
24) Hirose, K., Tajima, K., Hamajima, N., Inoue, M., Takezaki, T., Kuroishi, T., Yoshida, M. and Tokudome, S. A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. *Jpn. J. Cancer Res.*, **86**, 146–154 (1995).
25) Hu, Y.-H., Nagata, C., Shimizu, H., Kaneda, N. and Kashiki, Y. Association of body mass index, physical activity, and reproductive histories with breast cancer: a case-control study in Gifu, Japan. *Breast Cancer Res. Treat.*, **43**, 65–72 (1997).
26) Minami, Y., Ohuchi, N., Taeda, Y., Fukao, A. and Hisamichi, S. Risk factors for benign breast disease according to histopathological type: comparisons with risk factors for breast cancer. *Jpn. J. Cancer Res.*, **89**, 116–123 (1998).
27) Consensus Meeting. Is 'fibrocystic disease' of the breast precancerous? *Arch. Pathol. Lab. Med.*, **110**, 171–173 (1986).
28) Page, D. L., Anderson, T. J. and Rogers, L. W. Epithelial hyperplasia. *In* "Diagnostic Histopathology of the Breast," ed. D. L. Page and T. J. Anderson, pp. 120–156 (1987).
29) Page, D. L. and Simpson, J. F. Benign, high-risk, and premalignant lesions of the mamma. *In* "The Breast-comprehensive Management of Benign and Malignant Diseases," ed. K. I. Bland and E. M. Copeland III, pp. 113–134 (1991). W. B. Saunders Co., Philadelphia.
30) Rothman, K. J. "Modern Epidemiology," pp. 177–236 (1986). Little Brown, Boston.
31) Rosner, B. "Fundamentals of Biostatistics," 4th Ed., pp. 443–550 (1995). Duxbury Press, Belmont.
32) "SAS/STAT User's Guide, Release 6.03 Edition" (1988). SAS Institute Inc., Cary.
33) Sasano, N., Tateno, H. and Stemmermann, G. N. Volume and hyperplastic lesions of breasts of Japanese women in Hawaii and Japan. *Prev. Med.*, **7**, 196–204 (1978).
34) Black, M. M. and Chabon, A. B. *In situ* carcinoma of the breast. *In* "Pathology Annual," ed. S. C. Sommers, pp. 185–210 (1969). Appleton Century Crofts, New York.
35) Ohuchi, N., Page, D. L., Merino, M. J., Viglione, M. J., Kufe, D. W. and Schlom, J. Expression of tumor-associated antigen (DF3) in atypical hyperplasias and *in situ* carcinomas of the human breast. *J. Natl. Cancer Inst.*, **79**, 109–117 (1987).
36) Parkin, D. M., Whelan, S. L., Ferlay, J., Raymond, L. and Young, J. "Cancer Incidence in Five Continents," vol. VII (1988). Int. Agency Res. Cancer Sci. Publ., Oxford Univ. Press, Oxford.