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Hiroko Nakao*

*Okayama University,

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Abstract

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KEYWORDS: season of birth, breast cancer, menopausal status, reproductive history, risk factor

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Season of Birth of Breast Cancer Patients and Its Relation to Patients' Reproductive History in Tokyo, Japan

Hiroko Nakao*

Department of Hygiene, Okayama University Medical School, Okayama 700, Japan

Seasonal distribution of the birth dates of 405 pre-menopausal and 285 post-menopausal breast cancer patients was investigated in order to determine whether or not the season of their birth was related to various reproductive risk factors of breast cancer, including nulliparity, late age at first birth, early age at menarche, late age at menopause, and a history of benign breast diseases. The seasonal distributions of births were compared between groups of patients categorized according to whether they possessed each risk factor or not, separately for pre- and post-menopausal patients. Patients with the same menopausal status generally had the same seasonal distribution of births, irrespective of whether or not they possessed a risk factor. Moreover, low-risk patients exhibited more deviation in the seasonal distribution of birth from general births than the high-risk patients. These results suggest that the distinctive seasonal distribution of birth observed in breast cancer patients is basically a phenomenon independent from the effect of the reproductive history on the occurrence of breast cancer, and that specific seasonal factors are involved at the fetal or neonatal stage in the etiology of breast cancer.

Key words : season of birth, breast cancer, menopausal status, reproductive history, risk factor

It has been reported that a distinct seasonal deviation exists in the births of breast cancer patients in comparison with general births, suggesting the possibility that some exogeneous seasonal factors, which act at the fetal or neonatal stages, are involved in the etiology of breast cancer (1). Breast cancer patients were found to have a major peak of birth between spring and autumn and a trough in winter. However, the seasonal birth distributions were not identical among pre- and post-menopausal patient groups, even when the patients were born in the same birth-year period or had cancer of the same histologic type. This observation indicated that the occurrence and development of breast cancer in pre-menopausal women might have characteristics distinct from those in post-menopausal women,and that the different epidemiological features between

* To whom correspondence should be addressed.

pre- and post-menopausal breast cancer, which have been found by several investigators (2-4), could be attributed to differences in etiologic factors dependent on season of birth.

There have been many studies which have indicated the causal effects of physiological characteristics on the development of breast cancer. Many studies have suggested that reproductive history is well associated with an increase or decrease of the risk of breast cancer (5). According to these studies, breast cancer is more common among women who have never borne children than among parous women, and the longer a woman delays her first childbirth the greater the increased risk of developing the disease. It has also been reported that an early age at menarche and a late age at menopause carry an increased risk of breast cancer. A history of benign breast diseases has also been reported to be a risk factor for breast cancer.

It is therefore necessary to investigate the relationship between reproductive risk factors and the season of birth of breast cancer patients in order to confirm whether or not season of birth affect the occurrence of breast cancer. In the present study, comparisons were made of the season of birth between groups of breast cancer patients categorized according to whether or not they possessed each reproductive risk factor, separately for pre- and post-menopausal patients.

Materials and Methods

Subjects. The patients studied were from a population of 828 Japanese women admitted with breast cancer to two hospitals in Tokyo during the years 1963-1983 (1). One hospital was The First Surgical Department of The University of Tokyo, and the other was The National Medical Center of Hospital. The patients included in the study were 405 pre-menopausal women, with a mean age of 41.3 years at the first admission, and 285 post-menopausal women, with a mean age of 63.8 years, who had had no menstrual period in the 2 years prior to admission. Sixty-three peri-menopausal patients, 49 artificially menopaused patients, and 26 patients of unknown menopausal status were not included in the study. The pre-menopausal subjects were born during the period 1911-1965, and the post-menopausal subjects were born during the period 1881-1935. Their birth dates and reproductive histories were obtained from their case records kept in the respective hospitals.

Statistical analysis of season of birth. The distributions of the patients' month of birth were compared with those of a female control population, information about which was obtained from two sources: 1) a survey on the birth dates of 5,449 surviving members of the general population born during the period 1881-1900 (6), and 2) live births listed in the Japanese Vital Statistics since 1901. The control population after 1900 contained some people not living at this time. But previous investigations of season of birth of patients have usually compared the patients' birth distributions with general live birth distribution obtained from government vital statistics (7-13). The expected monthly birth figures were calculated from members of the control population born in the same birth-year period as the patients. A comparison between the observed and the expected distribution was made at first for each 5-birth-year period, and when the cases were unified over some 5-year periods, the control population was weighted according to the number of patients for each 5-year period.

The variance of the observed frequency distribution from the expected distribution was evaluated with the χ^2 test for a quarterly series equivalent to the four seasons (February to April, May to July, August to October, November to January) ($df = 3$). One seasonal deviation was also tested by the χ^2 test ($df = 1$) (1).

Reproductive histories and comparison of the season of birth between patient groups. The following parameters of the reproductive history were considered: parity, age at first birth, age at menarche, age at menopause in post-menopausal cases, and a history of benign breast diseases.

For each parameter of the reproductive history, the patients were divided into a low-risk or high-risk group according to their individual records (14). Some patients' records were not complete for all the parameters ("unknown" groups in Tables 1 and 2). However, the birth distribution of the unknown groups, except for "age at menarche", was not significantly different from that of the patients whose records were complete for each parameter. The season of birth was then compared between the low- and high-risk groups according to each parameter of the reproductive history, separately for pre- and post-menopausal patients. The season of birth was also compared in context with the reproductive history between pre- and post-menopausal patients born in the same birth-year period during 1916-1930. Statistical analysis of the comparisons of seasonal distributions of birth between patient groups was conducted by the χ^2 test ($df = 3$) for a quarterly series as mentioned above.

Results

Comparisons of season of birth between low- and high-risk groups. The monthly birth distributions of low- and high-risk groups for each parameter of the reproductive history are shown in Fig. 1 for pre-menopausal patients and in Fig. 2 for post-menopausal patients. The quarterly birth distributions are shown in Tables 1 and 2 for pre- and post-menopausal patients, respectively.

In pre-menopausal patients, an evident summer birth peak was observed in every low-risk group. The high-risk groups showed similar seasonal birth patterns to those of the low-risk groups, although the peak appeared a little later than in low-risk groups (Fig. 1). A statistical evaluation of the comparisons of the season of birth between low- and high-risk groups according to reproductive history is shown in Table 1. There were no significant differences in season of birth between low- and high-risk groups for any of the parameters of the reproductive history. With respect to post-menopausal patients, every low- and high-risk group showed one birth peak in the spring and another in the autumn and a trough in the summer and another in the winter (Fig. 2). For every parameter of the reproductive history, the distributions of the season of birth showed no significant difference between low- and high-risk groups (Table 2). There were many patients whose age at menarche was unknown. Their birth distribution was significantly different from that of the patients whose age at menarche was confirmed. But the latter patients, both pre- and post-menopausal, showed the same trend as mentioned above.

The low-risk groups of both pre- and post-menopausal patients exhibited more deviation in the distribution of season of birth from the general population in comparison with high-risk groups (Tables 1 and 2), except for pre-menopausal patients in the age at menarche category and post-menopausal patients in the age at first birth category.

Comparisons of season of birth between pre- and post-menopausal patients. The season of birth was compared between pre- and post-menopausal patients born in the same birth-year period during 1916-1930 according to parameters of their reproductive histories (Fig. 3). Every pre-menopausal patient group showed a clear summer birth peak and a winter trough. In contrast, every post-menopausal patient group had two distinct peaks, in the spring and autumn, and two troughs, in the summer and winter. These differences in season of birth between pre- and post-menopausal patients were significant in all low-risk groups (Table 3). In the high-risk groups, distinctive seasonal patterns of birth according to menopausal status were observed as in the low-risk groups, although the differences in the season of birth were not statistically significant.

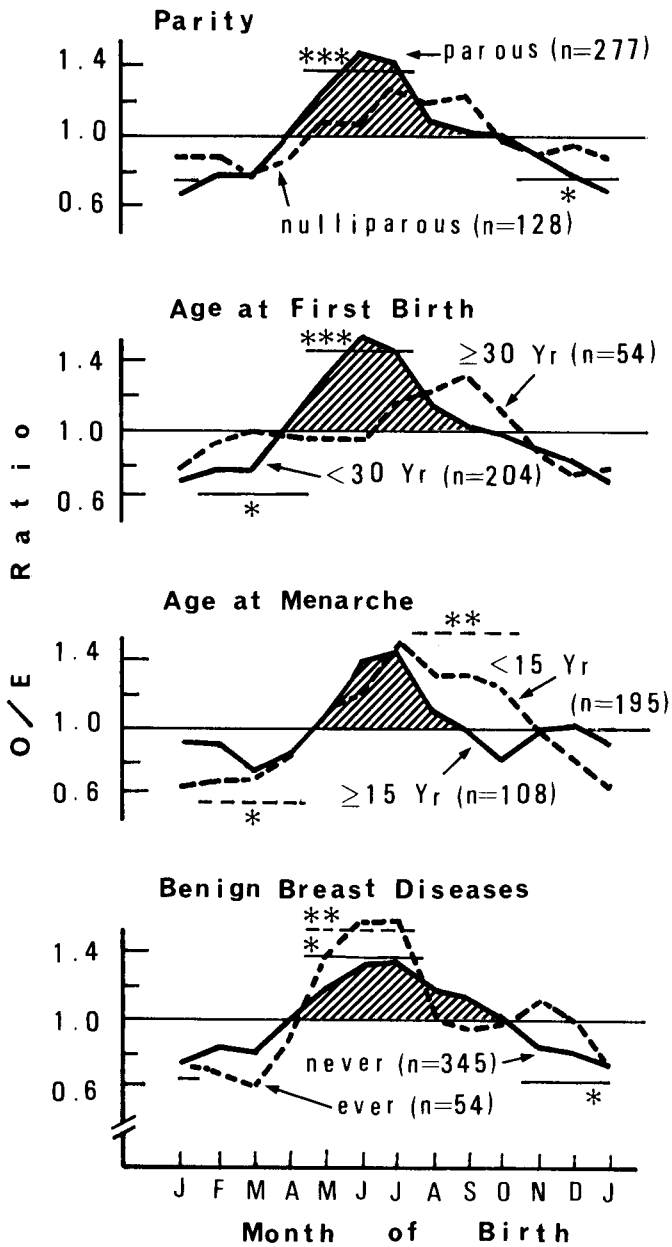

Fig. 1 Comparison of monthly variation of the observed/expected (O/E) ratio (3-months-moving average) between low- and high-risk groups according to each parameter of the reproductive history among pre-menopausal patients born between 1911 and 1965. The solid and dashed lines represent the low-risk groups and high-risk groups, respectively. The horizontal bars indicate significant deviations by χ^2 test (df = 1) of the observed birth distribution from the expected distribution. *: $p < 0.05$, **: $p < 0.01$, and ***: $p < 0.001$.

Discussion

There have been a number of epidemiologic studies concerning the effect of reproductive histories of women on the occurrence of breast cancer (5, 15-18). According to these studies, nulliparity, late age at first birth, early age at menarche, late age at menopause, and previous benign breast diseases have generally been considered to be risk factors of breast cancer. On the other hand, the possibility of the involvement of certain exogenous factors

Table 1 Statistical analysis of the differences in birth distribution between subjects and a control population, and between low- and high-risk subject groups, among pre-menopausal patients

Subject groups according to reproductive history	Birth months				Total	Test for seasonal deviation of births[b]	
	Feb-Apr	May-Jul	Aug-Oct	Nov-Jan		From control	Between low and high-risk groups
	n (Ob/Ex)[a]	n (Ob/Ex)[a]	n (Ob/Ex)[a]	n (Ob/Ex)[a]		χ^2 (3)	χ^2 (3)
All pre-menopausal patients	92/112.7	107/78.2	106/95.8	100/118.2	405	18.3***	.....
Parity							
Parous (low-risk)	63/77.2	80/53.4	69/65.5	65/81.0	277	19.2***	
Nulliparous (high-risk)	29/35.6	27/24.8	37/30.3	35/37.3	128	3.0	3.08 (n. s.)
Age at first birth, year		(Mean ± S. D.	26.6 ± 4.1)				
< 30 (low-risk)	44/56.7	62/39.4	49/48.2	49/59.7	204	17.8***	
≧ 30 (high-risk)	15/15.1	10/10.4	17/12.8	12/15.7	54	2.3	3.86 (n. s.)
Unknown	4	8	3	4	19		
Age at menarche, year		(Mean ± S. D.	14.1 ± 1.6)				
≧ 15 (low-risk)	23/30.5	28/20.6	25/25.4	32/31.6	108	4.6	
< 15 (high-risk)	39/53.8	47/38.0	62/46.3	47/56.9	195	13.3**	2.77 (n. s.)
Unknown[c]	30	32	19	21	102		
Benign breast diseases							
Never (low-risk)	81/96.0	88/66.7	93/81.6	83/100.7	345	13.8**	
Ever (high-risk)	9/15.1	17/10.4	12/12.8	16/15.8	54	6.8	2.58 (n. s.)
Unknown	2	2	1	1	6		

a: Ob, observed number; Ex, expected number calculated from members of the control population born in the same birth-year period as the patients.
b: χ^2 test for a quarterly series (df = 3). **: $p < 0.01$, ***: $p < 0.001$, (n. s.): not significant.
c: The birth distribution of the patients whose age at menarche was unknown was significantly different from that of the patients whose age at menarche was known ($p < 0.05$, χ^2 test (df = 3)).

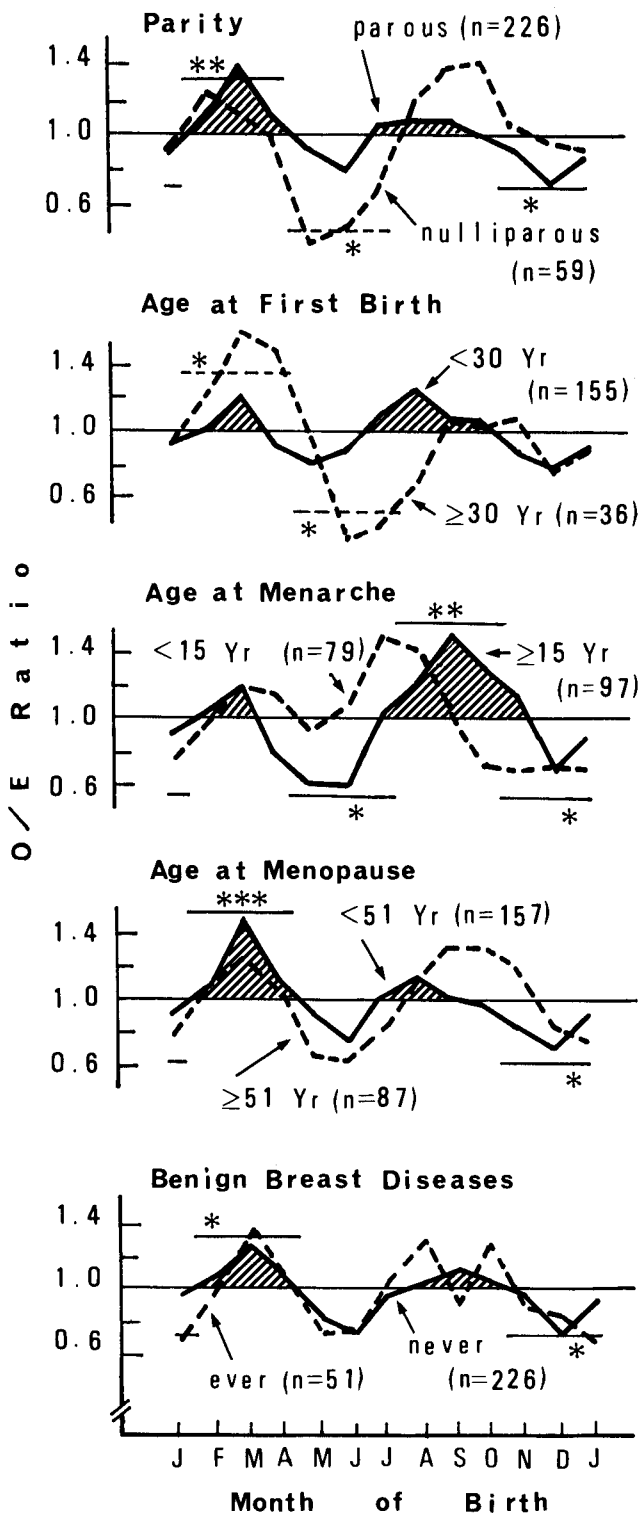

Fig. 2 Comparison of monthly variation of the observed/expected (O/E) ratio (3-months-moving average) between low- and high-risk groups according to each parameter of the reproductive history among post-menopausal patients born between 1881 and 1935. The solid and dashed lines represent the low-risk groups and high-risk groups, respectively. The horizontal bars indicate significant deviations by χ^2 test (df = 1) of the observed birth distribution from the expected distribution. *: $p < 0.05$, **: $p < 0.01$, and ***: $p < 0.001$.

Table 2 Statistical analysis of the differences in birth distribution between subjects and a control population, and between low- and high-risk subject groups, among post-menopausal patients

Subject groups according to reproductive history	Birth months				Total	Test for seasonal deviation of births[b]	
	Feb-Apr	May-Jul	Aug-Oct	Nov-Jan		From control $\chi^2(3)$	Between low and high-risk groups $\chi^2(3)$
	n (Ob/Ex)[a]	n (Ob/Ex)[a]	n (Ob/Ex)[a]	n (Ob/Ex)[a]			
All post-menopausal patients	105/80.3	42/57.5	76/67.3	62/79.9	285	16.9***	.....
Parity							
Parous (low-risk)	86/63.7	37/45.6	57/53.4	46/63.3	226	14.4**	
Nulliparous (high-risk)	19/16.6	5/11.9	19/13.9	16/16.6	59	6.2	4.25 (n. s.)
Age at first birth, year		(Mean ± S. D.	25.7 ± 4.4)				
< 30 (low-risk)	53/43.6	28/31.2	39/36.6	35/43.6	155	4.2	
≧ 30 (high-risk)	17/10.2	2/7.2	9/8.5	8/10.1	36	8.8*	4.27 (n. s.)
Unknown	16	7	9	3	35		
Age at menarche, year		(Mean ± S. D.	14.9 ± 1.8)				
≧ 15 (low-risk)	33/27.3	12/19.8	34/22.9	18/27.1	97	12.8**	
< 15 (high-risk)	27/22.3	17/15.8	19/18.7	16/22.3	79	2.9	4.03 (n. s.)
Unknown[c]	45	13	23	28	109		
Age at menopause, year		(Mean ± S. D.	49.4 ± 3.7)				
< 51 (low-risk)	65/44.3	24/31.5	38/37.1	30/44.1	157	16.1**	
≧ 51 (high-risk)	28/24.5	11/17.6	27/20.5	21/24.5	87	5.5	3.18 (n. s.)
Unknown	12	7	11	11	41		
Benign breast diseases							
Never (low-risk)	81/63.8	34/45.6	62/53.3	49/63.3	226	12.3**	
Ever (high-risk)	20/14.3	8/10.3	11/12.1	12/14.4	51	3.2	0.75 (n. s.)
Unknown	4	0	3	1	8		

a: Ob, observed number; Ex, expected number calculated from members of the control population born in the same birth-year period as the patients.
b: χ^2 test for a quarterly series (df = 3). *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, (n. s.): not significant.
c: The birth distribution of the patients whose age at menarche was unknown was significantly different from that of the patients whose age at menarche was known ($p < 0.05$, χ^2 test (df = 3)).

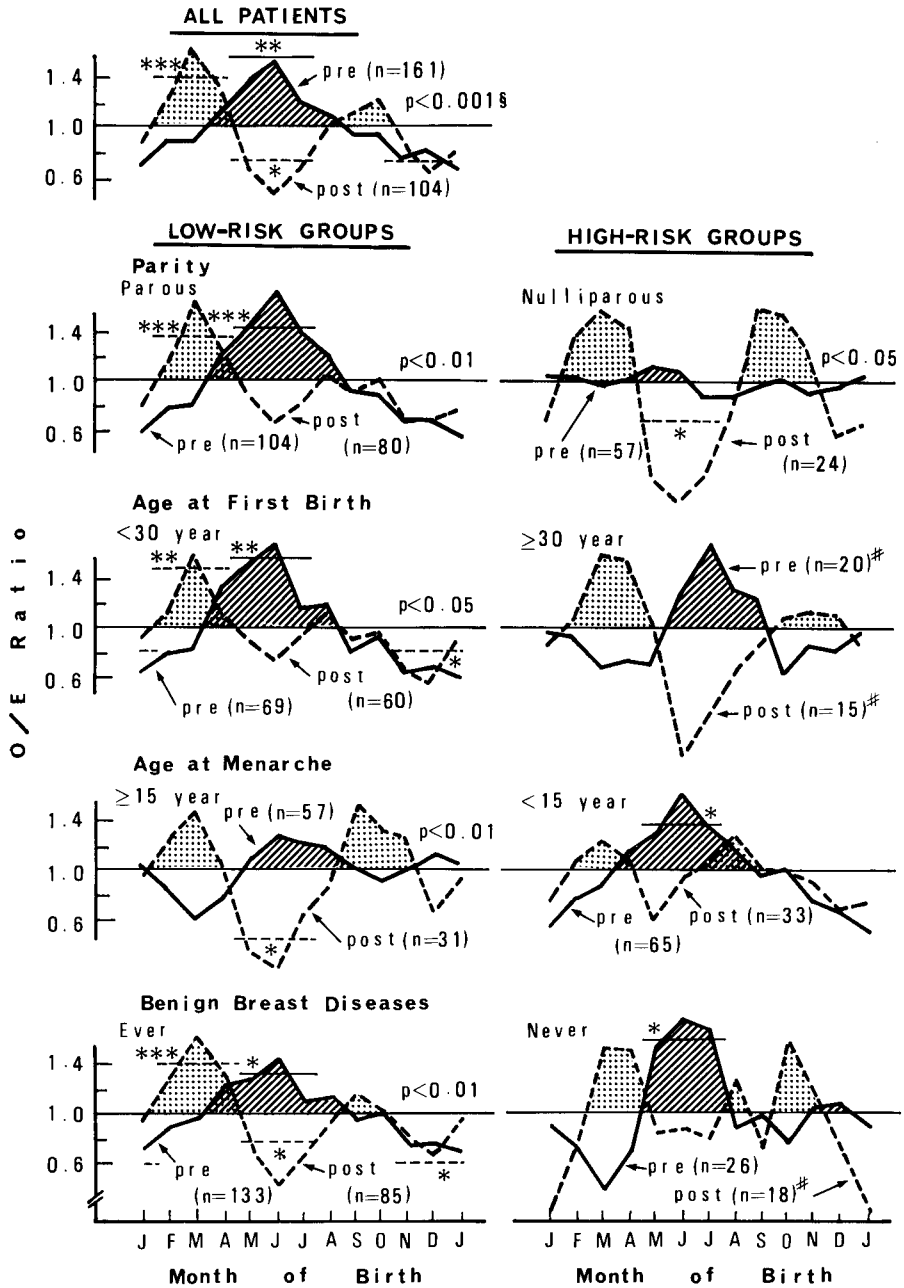

Fig. 3 Comparison of monthly variation of the observed/expected (O/E) ratio (3-months-moving average) between pre- and post-menopausal patient groups born in the same birth year period during 1916-1930. The solid and dashed lines represent the low-risk groups and high-risk groups, respectively. The horizontal bars indicate significant deviations by χ^2 test (df = 1) of the observed birth distribution from the expected distribution. *: $p < 0.05$, **: $p < 0.01$, and ***: $p < 0.001$. This χ^2 test was not performed on the patient groups marked with "#", because the number of patients was too small for the χ^2 test. §: The p values indicate significant differences in birth distribution between pre- and post-menopausal groups evaluated by χ^2 test for a quarterly series (df = 3) (see Table 3 for details).

Table 3 Comparison of the season of birth between pre- and post-menopausal patients born in the same birth-year period during 1916-1930 according to parameters of their reproductive histories

Reproductive history		Birth months					Between pre and post χ^2 (3)[a]			Birth months					Between pre and post χ^2 (3)[a]
		Feb-Apr	May-Jul	Aug-Oct	Nov-Jan	Total				Feb-Apr	May-Jul	Aug-Oct	Nov-Jan	Total	
		n	n	n	n					n	n	n	n		
All patients	pre-	41	46	36	38	161									
	post-	48	10	26	20	104	19.5***								
		Low-risk groups								High-risk groups					
Parity															
Parous	pre-	25	34	23	22	104		Nulliparous	pre-	16	12	13	16	57	
	post-	37	10	17	16	80	14.4**		post-	11	0	9	4	24	8.9*
Age at first birth, year															
< 30 year	pre-	17	23	15	14	69		≧ 30 year	pre-	4	5	6	5	20	
	post-	28	9	13	10	60	9.0*		post-	7	0	3	5	15	3.0[b]
Age at menarche, year															
≧ 15 year	pre-	10	14	14	19	57		< 15 year	pre-	17	20	15	13	65	
	post-	13	1	11	6	31	12.2**		post-	12	6	8	7	33	2.1
Benign breast diseases															
Never	pre-	37	36	30	30	133		Ever	pre-	3	9	6	8	26	
	post-	39	7	23	16	85	15.0**		post-	8	3	3	4	18	1.6[b]

a: χ^2 test for a quarterly series (df = 3). *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.
b: χ^2 test with Yates' correction for a half year (Feb-Oct and Nov-Apr) series (df = 1). The number of the patients was too small for the χ^2 test for a quarterly series (df = 3).

seasonally acting at the fetal or neonatal stages in the etiology of breast cancer was recently hypothesized by the author (1), who showed a distinct seasonal trend in the birth of breast cancer patients.

In the present study, the relationship between the season of birth of breast cancer patients and certain parameters in their reproductive histories indicating a risk of developing breast cancer was examined. It was found that patients with the same menopausal status generally had the same seasonal characteristics of birth, irrespective of whether they possessed a high-risk or low-risk reproductive history. The pre-menopausal patients had a birth-peak in summer and a trough in winter, and the post-menopausal patients showed two peaks, in the spring and autumn, and two troughs, in the summer and winter. These seasonal characteristics of birth agreed satisfactorily with those previously reported (1). Moreover, the seasonal deviation of birth was more clearly observed in the patients having low-risk reproductive histories than in the high-risk patients. Therefore, it can be concluded that the distinctive seasonal characteristics of birth observed in breast cancer patients is basically a phenomenon independent from the effect of the reproductive history on the occurrence of breast cancer. These results lend support to the existence of etiologic factors of breast cancer related to season of birth. It has been reported that newborn and very young laboratory animals are more susceptible to many cancer-producing factors than older ones (19). If so, it is possible that, at the fetal or neonatal stage, women born between spring and autumn have an increased risk of encountering certain exogenous etiologic factors for breast cancer than those born in winter, irrespective of whether or not they acquire risks for this form of cancer in their later reproductive lives.

In the present study, a different distribution of birth season was apparent between pre- and post-menopausal patient groups, even when the patients were born in the same birth-year period and their reproductive histories had the same features. The difference in birth season according to menopausal status thus proved to have no relationship with the reproductive history. These findings suggested that there could be two different etiologic factors acting at the fetal or neonatal stage, one relating to the occurrence of pre-menopausal breast cancer and the other to that of post-menopausal breast cancer (1).

From the results of this study, a hypothesis can be proposed that etiologic factors acting at the fetal or neonatal stage may play a role in either initiating breast cancer or changing the tissue's susceptibility to oncogenic factors, and that risk factors present in a patient's reproductive history (5, 15-18), and perhaps factors concerned with diet (20) or body weight (21), may work as cancer-promoting factors in the breast.

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