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Birth Seasonality of Breast Cancer Patients and its Variation According to Menopausal Status and Histologic Type in Japan

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Abstract—*The season of birth of* 828 *Japanese female patients with breast cancer was compared with that of a general control population. A distinct seasonal deviation was detected in the birth of breast cancer patients. In general, a major peak of birth occurred during spring to autumn, and a trough appeared in winter. However, the birth seasonal distributions of pre- and post-menopausal patients groups were not identical. The pre-menopausal patients had a summer birth excess and a clear sinusoidal distribution. The post-menopausal patients showed two peaks in spring and autumn. Such differences according to menopausal status were consistently observed when patients were divided by birth-year period and by histological subtype. These findings suggest the possibility of involvement of some exogenous seasonal factors acting at the fetal or neonatal stages in the etiology of breast cancer, and that the characteristics of the development of breast cancer differ in pre-menopausal women in comparison with those in post-menopausal women.*

INTRODUCTION

SEASONAL birth variations of patients have been described for several, presumably non-congenital, chronic diseases of unknown etiology including cancers [1–5] as well as schizophrenia [6–7] and diabetes [8]. When the monthly birth distribution of a group of patients exhibits seasonal deviation from that of a control population, an exogenous seasonal factor exerting its effect at the fetal or neonatal stage can be considered in the etiology of that disease.

In the case of breast cancer, it is known that the mouse mammary tumor virus (MuMTV) causes the tumor when it is transmitted to neonatal mice via milk [9]. Therefore, it is likely that human breast cancer may be associated with some events occurring at an early stage of life. The present study examined the possible effect of some exogenous factors acting at the fetal or neonatal stage on the incidence of breast cancer by investigating the birth seasonality of patients.

Several studies have noted that the etiologic risk factors and the appearance rate of histologic types [10] in pre-menopausal breast cancers are distinct from those in post-menopausal cases. Nulliparity and late first parity appear to increase the risk of breast cancer among older women [11, 12], and a family history of breast cancer is more regularly observed among young pre-menopausal patients [13]. It is supposed that birth seasonality may also be different between pre- and post-menopausal patients. Therefore the monthly birth statistics for a group of breast cancer patients were investigated in relation to the patients' menopausal statuses and histologic types for comparison between pre- and post-menopausal patients.

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MATERIALS AND METHODS

Patients

The patient population was composed of 828 Japanese women admitted for breast cancer to two hospitals in Tokyo during the years 1963–1983. Four hundred and ten cases were from The First Surgical Department, The University of Tokyo, and the other 418 cases were from The National Medical Center of Hospital. Their birth dates, menopausal statuses, reproductive histories, and histologic diagnoses were obtained from their clinical records. Their birth dates were recorded on the basis of their birth registrations at respective government offices, and were compared with birth data of a control population. The patients were born during the period 1881–1965.

Histologic classification

Each case was histologically diagnosed according to the criteria recommended by The Japan Mammary Cancer Society [14]. This classification is fundamentally the same as the WHO classification with a subclassification of the common breast-cancer type. Infiltrating common-type carcinoma has three subgroups: papillotubular, medullary tubular, and scirrhous carcinoma.

Statistical analysis

The monthly birth distributions of the patients were compared with those of a female control population which was obtained from two sources: (1) a survey on the birth dates of 10,938 surviving members of the general population born during the period 1881–1900 [15], and (2) live births listed in the Japanese Vital Statistics since 1901. The expected monthly birth figures were calculated from members of the control population born in the same birth-year period as the patients. A basic comparison between the observed and the expected distribution was made for each 5-birth-year period, and when the numbers were totalled over some periods, the control population was weighted according to the number of patients for each 5-yr period.

The variance of the observed frequency distribution from the expected distribution was evaluated through χ^2 tests for an individual monthly series ($df = 11$) and 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 χ^2 test ($df = 1$). Compatibility with the significance of sinusoidal seasonality was tested, and when detected, the month of the peak was estimated according to the method of Walter and Elwood [16].

Patients' subgroups submitted to analysis

The patients were divided into four groups of pre-, peri-, post-, and artificially menopausal patients according to their menopausal statuses at the first admission for breast cancer. Patients who had had no menstrual period in the 2 yr prior to admission were defined as post-menopausal. Patients who had undergone menopause due to gynecological diseases were defined as artificially menopausal.

Monthly birth distributions were compared between the two hospitals for the same menopausal status group, and the patients from these hospitals showed almost identical monthly distributions for the same menopausal status. The monthly birth frequencies were thus combined with regard to menopausal status for the two hospitals.

Birth seasonality was investigated at first in the entire group of 828 patients, and then in each menopausal status group. The birth seasonal variation by histologic type was analysed in the pre- and post-menopausal patients, because the numbers of peri- and artificially menopausal patients were too small to be analysed.

RESULTS

The monthly birth distributions of all patients and the control population are given in Table 1, and the monthly ratio of the observed to the expected number of births is shown in Fig 1-(1). The birth distribution of all patients was found to be significantly different from the expected distribution not only by the monthly series analysis but also by the quarterly series analysis (Table 1). The patients' birth distribution had an evident winter trough between November and January ($\chi^2(1) = 11.35$, $P < 0.001$) and a regular sinusoidal seasonality with an estimated peak in mid-July.

The patients were divided into four menopausal groups. The numbers of cases in pre-menopausal, peri-menopausal, post-menopausal, and artificially menopausal groups were 405, 63, 285, and 49, respectively. When the monthly birth distribution was investigated by menopausal group, every group exhibited a birth distribution distinct from the expected one, and a winter trough common to them. The pre- and post-menopausal groups exhibited significantly different distributions from the expected distribution in the monthly series

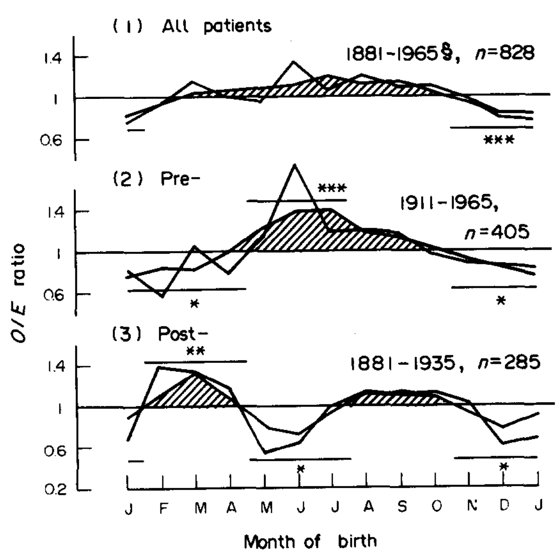

Fig. 1. Monthly ratio of the observed to the expected number of births (O/E ratio). The thin lines represent the monthly O/E ratio. The thick lines represent the 3-month-*moving average O/E ratio. The horizontal bars indicate significant deviations of the observed birth distribution from the expected distribution showing a significant level by* χ^2 *test* (df = 1), $*$:$P < 0.05$, $**$:$P < 0.01$, *and* $***$:$P < 0.001$. *§Birth-year period of patients.*

Table 1. Monthly numbers of observed and expected births for all patients and for each menopausal group

Month of birth	Control†	All Obs.	All Exp.	Pre- Obs.	Pre- Exp.	Post- Obs.	Post- Exp.
January	519,697	85	113.8	48	58.5	25	36.0
February	377,228	73	79.1	23	39.0	37	26.8
March	416,328	104	92.3	46	44.3	43	32.1
April	310,019	60	60.9	23	29.5	25	21.3
May	285,184	53	56.1	30	26.7	11	20.2
June	268,428	67	51.3	45	24.6	12	18.3
July	294,797	58	55.0	32	27.0	19	19.0
August	324,780	75	63.0	37	30.7	25	21.8
September	330,840	71	65.3	37	31.9	25	22.5
October	337,099	73	67.2	32	33.1	26	22.9
November	340,916	67	69.2	30	34.3	24	23.4
December	289,902	42	54.9	22	25.5	13	20.5
Total	4,095,218	828	828	405	405	285	285
Mean age of cases ± S.D.		51.0 ± 12.4		41.3 ± 6.1		63.8 ± 8.1	
Monthly‡ $\chi^2(11)$		20.73*		31.37***		21.80*	
Quarterly§ $\chi^2(3)$		11.35**		18.30***		16.91***	
Regular sinusoidal seasonality $\chi^2(2)$		11.2**		18.2***		0.1	
Month of peak		mid-July		mid-July		–	

Obs. = Observed number; Exp. = expected number; $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.
†Total births in Tokyo during the period 1881–1965. Each expected birth distribution was calculated from a control group, adjusting the birth-year period and the composition ratio of the number of births in each 5-birth-year period to those of the patient group.
‡Monthly series analysis by χ^2 test (between Obs. and Exp. distributions).
§Quarterly series analysis by χ^2 test (between Obs.and Exp. distributions).

analysis and in the quarterly series analysis (Table 1). Furthermore, deviation from the expected birth distribution was more clearly detected in the pre- and post-menopausal groups than in the total group of patients (Table 1).

However, the birth seasonal distributions were not identical between the pre- and post-menopausal groups (Fig. 1-(2)(3)). In the pre-menopausal group, a significant birth peak was observed between May and July ($\chi^2(1) = 13.11$, $P < 0.001$) and a significant trough between November and April ($\chi^2(1) = 7.52$, $P < 0.01$). In the post-menopausal group, a significant peak was found between February and April ($\chi^2(1) = 10.55$, $P < 0.01$) and two troughs were found between May and July ($\chi^2(1) = 5.42$, $P < 0.05$) and between November and January ($\chi^2(1) = 5.58$, $P < 0.05$). Regular sinusoidal seasonality was detected only in the pre-menopausal group with an estimated peak in mid-July (Table 1). Both menopausal groups had a winter trough between November and February, but the pre-menopausal group had a summer peak between May and July, when the post-menopausal group had a trough.

The birth seasonal characteristics of each menopausal group shown in Fig. 1 could be observed in almost every birth-year period (Fig. 2). The distinctive birth distributions of the pre- and post-menopausal groups were also detected among the

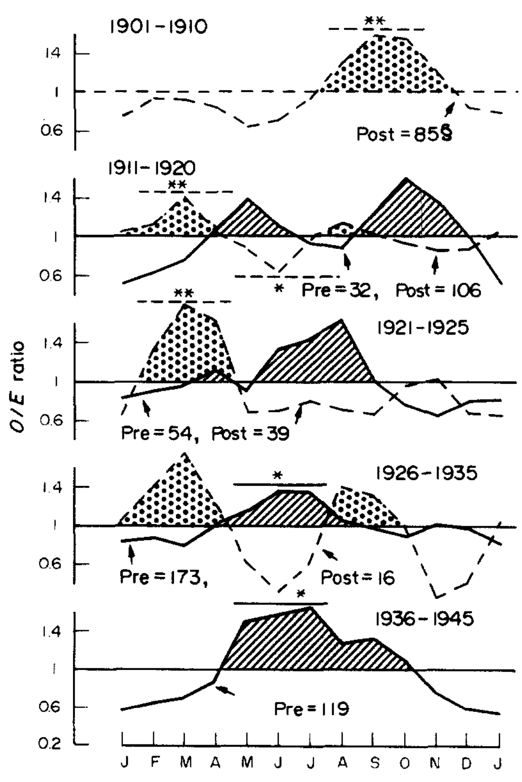

Fig. 2. Monthly variations of O/E ratio by birth-year period and comparisons of birth distributions between pre- and post-menopausal groups. The solid and dashed lines represent the 3-month- *moving average O/E ratios of pre- and post-menopausal groups, respectively. The horizontal bars indicate significant deviations of the observed birth distribution from the expected distribution showing a significant level by* χ^2 *test* (df = 1), $*:P < 0.05$, *and* $**:P < 0.01$. *§Number of patients.*

patients born in the same birth-year periods (1911–1935). Significant differences were found between the distributions of the two menopausal groups, born in the 1911–1935 periods, by χ^2 tests for monthly ($\chi^2(11) = 32.69$, $P < 0.005$) and for quarterly ($\chi^2(3) = 22.51$, $P < 0.001$) examination.

Table 2 presents the distribution of histological types in the pre- and post-menopausal patients. In both menopausal groups, more than 80% of the patients were histologically diagnosed as having invasive ductal carcinoma, of which the scirrhous type was most common. There were seven cases of invasive lobular carcinoma which is a rare type in Japan.

The birth seasonalities were investigated by histologic subtype and menopausal status among the patients with invasive ductal carcinoma. Table 3 presents the results of statistical tests on the deviation of the observed birth distribution from the expected distribution for each status group. Observed birth distributions were found to be significantly different from the expected ones by quarterly series analysis except for the scirrhouse-premenopausal group and the papillotubular-postmenopausal group. Figure 3 shows the monthly variations of O/E ratio in each subtype and menopausal group. Similar birth distributions were seen within the same menopausal groups rather than within the same histologic-subtype groups. In all the premenopausal groups, a peak was found in summer. The papillotubular- and medullotubular-premenopausal groups had a regular sinusoidal seasonality with estimated peaks in early August and mid-June, respectively (Table 3). All the postmenopausal groups had two peaks in spring and autumn, and only in the medullotubular-postmenopausal group was a regular sinusoidal seasonality detected with an estimated peak in mid-March.

Table 2. Distribution of the breast cancer patients by histologic type and menopausal status

Diagnostic classification	Pre-	Post-
Noninvasive		
Intraductal carcinoma	11	9
Lobular carcinoma *in situ*	0	0
Invasive		
Invasive ductal carcinoma	324	232
Subtype		
(1) Papillotubular	88	49
(2) Medullotubular	51	47
(3) Scirrhous	170	129
(1) + (3)	8	1
(2) + (3)	2	2
Unknown subtype	5	4
Invasive lobular carcinoma	5	2
Mucinous carcinoma	10	3
Medullary carcinoma	15	10
Tubular carcinoma	0	0
Adenoid carcinoma	0	0
Secretory carcinoma	0	0
Apocrine carcinoma	0	0
Squamous cell carcinoma	1	3
Others	0	0
Paget's disease	1	4
Unknown histologic type	38	22
Total	405	285

DISCUSSION

Bailar and Gurian analyzed the birth seasonal distributions of nearly 20,000 cancer deaths in the U.S. including 1820 cases of breast cancer and concluded that no relationship could be found between the occurrence of any cancer and the season of birth [4]. However, Dalén reported that when he recalculated their data, he obtained a significant deviation in the birth season of patients dying from cancer [17]. Jansson and Malahy briefly reported the birth season of breast cancer to be deviated in the U.S. [18]. In the present study, a distinct birth seasonal deviation was revealed in breast cancer patients in Japan, a consistent winter trough in seasonal births being found in every patient group.

The general demographic characteristics of women affected with breast cancer in Western countries are well known. The incidence rates of breast cancer vary with race and social class even within a single country [19]. However, the Japanese people consist of mostly a single ethnic group, and distinct social classes do not exist for practical purposes in Japan. Therefore, these demographic factors cannot be considered to have had an effect on the birth seasonal deviation of breast cancer patients in this study.

The results suggest the possibility of involvement of certain exogenous factors seasonally acting at the fetal or neonatal stages in the etiology of breast cancer. Perinatal infection with certain viruses is known to increase the incidence of Burkitt's lymphoma in man [20] and mammary tumor in mice [21]. Hence, it is likely that new-born human infants or those in the perinatal stage would be more susceptible to some cancer-producing factors than older humans. In such cases, neonates born during a certain season, spring to autumn, appear to have an increased risk of encountering certain etiologic events concerned with breast cancer compared with those born in winter.

The present results also show that birth seasonal distributions are not identical among pre- and post-menopausal patient groups, even when the patients are born in the same birth-year period or are of the same histologic type. The pre-menopausal patient group consistently had a summer

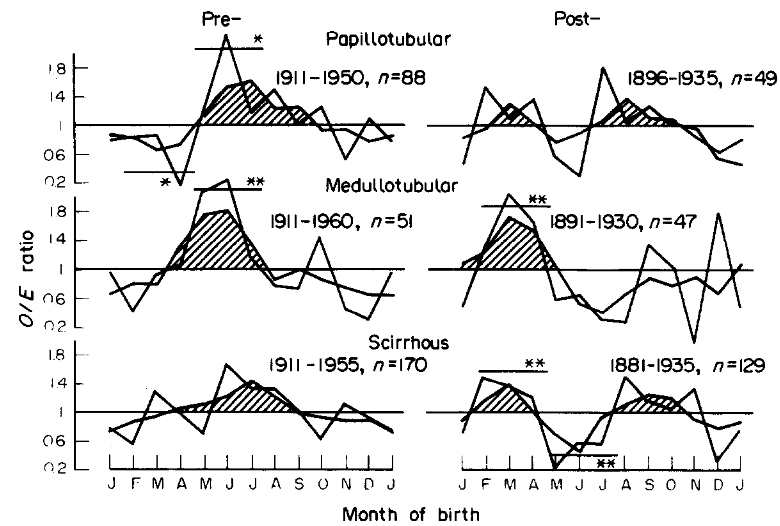

Fig. 3. Monthly variations of O/E ratio by histologic subtype and menopausal status. The thin lines represent the monthly O/E ratio. The thick lines represent the 3-month-*moving average O/E ratio. The horizontal bars indicate significant deviations of the observed birth distribution from the expected distribution showing a significant level by* χ^2 *test* (df = 1), *:$P < 0.05$ *and* **:$P < 0.01$.

Table 3. The results of statistical analysis of the deviation of observed birth distribution from the expected birth distribution for each subtype and menopausal group

Subtype-menopausal group	Monthly series $\chi^2(11)$	Quarterly series $\chi^2(3)$	Sinusoidality $\chi^2(2)$	Month of peak
Pre-				
Papillotubular (88†)	17.85	10.00*	6.4*	early August
Medullotubular (51)	14.57	8.66*	7.2*	mid-June
Scirrhous (170)	15.98	2.23	5.3	–
Post-				
Papillotubular (49)	8.82	3.27	0.2	–
Medullotubular (47)	20.18*	10.34*	7.6*	mid-March
Scirrhous (129)	23.40*	16.00**	1.1	–

†Number of cases; – = No sinusoidality could be detected.
*$P < 0.05$; **$P < 0.01$.

peak and a winter trough in birth seasonality. In contrast, the birth seasonal distribution of the post-menopausal patient group showed peaks in spring and autumn and had two troughs in summer and winter. This observation indicates that the occurrence and development of breast cancer in pre-menopausal women may have distinct characteristics from that in post-menopausal women, and supports previous studies showing the different characteristics of etiologic risk factors and epidemiologic features of pre-menopausal, in comparison with post-menopausal, breast cancer [19]. It has been reported that nulliparity, late first parity [11, 12], and obesity [19] seem to increase the risk of breast cancer only for post-menopausal, older women. Pre-menopausal patients have a lower incidence of cytosolic estrogen receptor-positive tumors as well as quantitatively lower tumor levels of estrogen receptor compared with post-menopausal patients [22, 23]. Therefore, pre-menopausal breast cancer does not seem to be much influenced by reproductive modifications or hormonal conditions in later life and its development may be pre-determined at a much earlier stage of life than is the case for post-menopausal breast cancer.

We may consider several explanations for these phenomena. One is that there are two different factors acting at the fetal or neonatal stage, summer-type and spring-autumn-type factors, which are related to pre- and post-menopausal breast cancer, respectively. If this is so, the summer-type factor possibly has very strong oncogenic potential for more rapid tumor development in the pre-menopausal stage. The second is that the difference of pre- and pot-menopausal breast cancer results from differences of endogenous condition among women born in different seasons of the year, as suggested by observed differences in menarcheal ages among different birth seasonal groups [24].

Further studies are to be conducted with greater emphasis on the analysis of risk factors such as reproductive histories and body sizes of patients.

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