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Seasonality in the Occurrence of Breast Cancer[1]

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ABSTRACT

A nationwide study of all 3183 female patients with breast cancer in Israel diagnosed over a 7-year period (1960 to 1966) was conducted. Monthly series analysis showed a clear seasonal pattern in the symptomatology of the disease most pronounced in patients younger than 55 years, in all ethnic groups, mainly confined to cases with a nonlocalized tumor at diagnosis. Peaks occurred during spring, and troughs appeared during autumn. It is suggested that the pattern is of endogenous, probably hormonal nature, although environmental factors cannot be excluded.

INTRODUCTION

Seasonal variations have been described in the incidence of a number of noninfectious disorders such as chromosomal aberrations (14), congenital dislocation of the hip (4, 5), and insulin-dependent juvenile diabetes (9). The 2 latter diseases show mirror image patterns on the Northern *versus* Southern Hemisphere (4, 7, 9). Seasonality has also been associated with a number of hormonal-related characteristics, *e.g.*, duration of menstrual cycle, onset of menarche, and birth rate (19). Since various hormonal factors have been related to the etiology of breast cancer, it seemed of interest to investigate the potential presence of a seasonality pattern in breast cancer incidence.

MATERIALS AND METHODS

Study Population and Data Collection. The study is based on all female breast cancer cases diagnosed in Israel over the 7-year period of 1960 to 1966. During this period, 3,183 women with breast cancer were diagnosed (incidence of 42.7 per 100,000 women). Of these, 2,948 women (92.6%) had histopathological confirmation. Cases for whom histopathological diagnosis was not available were considered "probable" and were excluded from this analysis.

Cases were identified primarily through the Israel Tumor Registry and supplemented by the medical record files of all general hospitals in Israel. Data regarding demographic, reproductive, and medical information were abstracted from the original record.

Date of first symptom could be obtained for 66% of the patients. A comparison between patients with a recorded first symptom and the total study population showed that the distribution by ethnic origin was the same for the 2 groups, but there was a trend for less self-detection with increased age.

Statistical Analysis. The variation in the monthly frequencies of diagnosis and first symptom of breast cancer over the 7 years was examined through a trend analysis of annual data and a χ^2 test for homogeneity. No particular trend was found in the annual frequencies. The χ^2 test for homogeneity did not show ($p > 0.13$) a significant difference among the 7 years. Monthly frequencies were thus accumulated over the 7-year period. Analysis was performed on 2 types of series, individual monthly series and quarterly series equivalent to the 4 seasons.

The presence of seasonal pattern in the monthly data was studied through the model of Edwards (8) which is given by

$$p_i = \frac{1}{12}\left[1 + \beta \sin\left(\frac{2\pi i}{12}\right) + \beta_2 \cos\left(\frac{2\pi i}{12}\right)\right] \quad (i = 1, 2, \ldots, 12)$$

where p_i is the probability of a case in Month i. The 2 parameters of the model were estimated by a weighted least squares method. The fit of the model to the data was assessed by the χ^2 statistic for goodness of fit. The statistic is approximately distributed as χ^2 with 9 degrees of freedom when the model fits the data. When Edwards' model did not fit the data, the difference in the frequency distribution of the 4 seasons was evaluated through a χ^2 test for uniformity.

The significance of the sinusoidal seasonal trend was tested by the score statistic of Roger (20), which is approximately distributed as χ^2 with 2 degrees of freedom even for small sample size under the assumption of no seasonal trend.

The ratio of the highest predicted monthly frequency to the lowest one and that of Roger's statistic to the sample size were used as measures for the magnitude of the seasonal trend.

RESULTS

Table 1 and Chart 1 present the monthly frequency distribution of all cases by month of diagnosis, month of first symptom, and age. The data show a clear spring peak, both for time of diagnosis and of first symptom, with close to 20% of the cases occurring in May and June; the data also show a second peak for time of diagnosis at the fall. The latter peak may reflect the backlog of cases who postponed their admission during the 2 preceding months due to the Jewish high holidays. Thus, while 51% of the total series were hospitalized within 2 months of first symptom, this was true for only 29% of these hospitalized during the holiday months. Edwards' model for seasonal pattern was fitted to each series. The χ^2 statistic for goodness of fit (χ^2_{GF}) indicates that the series of months of diagnosis does not exhibit sinusoidal seasonal pattern, when all ages and each of the 2 age groups (under 55, 55+) are considered. However, when analyzed by quarters (March to May, June to August, September to November, December to February), a seasonal difference (high in June to August, low in September to November) is present ($p < 0.025$) for the total series and for the under-55 years of age category ($p < 0.05$), but not for the 55+ age group ($p > 0.30$).

On the other hand, the χ^2_{GF} statistic indicates that Edwards' model fits well the monthly series of first symptom for all ages ($p > 0.90$) and for the under-55 ($p > 0.80$) and 55+ age groups ($p > 0.45$) separately. Roger's test shows that the

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Table 1

Frequency distribution of all breast cancer cases in Israel (1960 to 1966) by month of diagnosis, month of first symptom, and age

	No. of cases																
	January	February	March	April	May	June	July	August	September	October	November	December	Total	χ^2_{GF}	$p(\chi^2)$	R	$p(R)$
Diagnosis																	
<55 yr	152	125	135	121	181	171	157	159	104	140	165	138	1748	34.3	<0.005	[a]	[a]
55+ yr	96	88	96	103	116	111	113	89	76	87	116	109	1200	17.87	<0.05	[a]	[a]
All ages	248	213	231	224	297	282	270	248	180	227	281	247	2948	45.35	<0.005	[a]	[a]
First symptom																	
<55 yr	94	95	109	110	114	126	117	97	82	79	88	92	1203	4.68	>0.80	19.14	<0.0005
55 + yr	61	63	54	85	76	64	55	59	54	62	52	56	741	9.55	>0.45	6.93	<0.05
All ages	155	158	163	195	190	190	172	156	136	141	140	148	1944	3.79	>0.90	26.28	<0.0005

[a] $p < 0.05$; therefore, Roger's test is not appropriate (18).

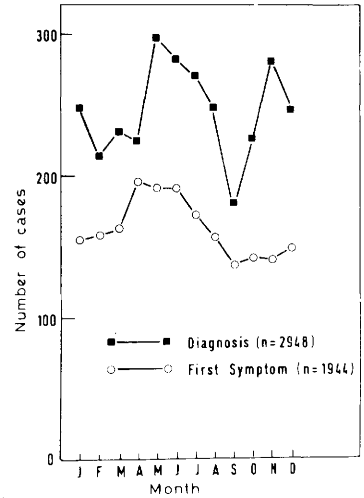

Chart 1. Frequency distribution of all breast cancer cases in Israel (1960 to 1966) by months of diagnosis, month (*abscissa letters*) of first symptom, and age.

sinusoidal seasonal trend in these series is highly significant when all ages ($R = 26.28$; $p < 0.0005$) and the under-55 age group ($R = 19.14$; $p < 0.0005$) are examined and somewhat less significant ($R = 6.93$, $p < 0.05$) for the 55+ age group.

Since the presenting symptoms are heterogeneous with a certain element of subjectiveness, further analysis was limited to the group of patients presenting with a lump in the breast. This was by far the largest group (94.4%) of the cases with known first symptom.

Table 2 presents the frequency distribution of cases by month, type of first symptom, and age, demonstrating that the seasonality effect reflects primarily the patients whose first symptom consisted of a breast lump. Furthermore, the χ^2 goodness-of-fit statistic shows that the model fits the cases presenting with a lump well ($p > 0.80$) but does not fit ($p < 0.005$) the no-lump series. The latter series shows, however, a seasonal difference (high in June to August, low in September to November) when analyzed by quarters ($\chi^2_3 = 28.23$; $p < 0.0001$). Roger's test shows that the sinusoidal seasonal pattern is highly significant ($R = 14.30$; $p < 0.0005$) for the patients presenting with a lump in the under-55 age group, but much less evident ($R = 4.63$, $p < 0.10$) in the older subjects. A 3-month moving average of the ratio of the observed number of the cases presenting with a lump to the expected number (the sum of the cases for each individual year divided by 12) for the under-55 age group is presented in Chart 2. The fall of the ratio in late 1966 cannot be explained and may be due to chance. The graph and the fitted model indicate a high incidence during spring with peaks in April and May and lows in the autumn with troughs in October and November. The ratio of highest to lowest predicted monthly frequency is 1.37 ± 0.69 (S.E.) in the under-55 age group, and 1.22 ± 1.3 in the 55+ age group. The ratio of Roger's statistic to the sample size is about twice as high in the younger age group as in the older one. Both results show that the magnitude of seasonal trend is stronger in the under-55 age category.

To delineate a spurious association, for instance lighter dressing or more frequent shower taking during the summer, the data were reanalyzed for patients for whom the time lapse between detection and diagnosis was at most 3 months. Similar

Table 2
Frequency distribution of breast cancer cases in Israel (1960 to 1966) by month, type of first symptom, and age

	No. of cases																
	January	February	March	April	May	June	July	August	September	October	November	December	Total	χ^2_{GF}	$p(\chi^2)$	R	p(R)
Lump in the breast																	
<55 yr	86	92	102	107	107	119	102	90	80	79	86	89	1139	3.30	>0.90	14.36	<0.0005
55+ yr	56	60	53	76	75	60	51	54	53	62	52	54	706	8.65	>0.40	4.63	<0.10
All ages	142	152	155	183	182	179	153	144	133	141	138	143	1845	4.33	>0.80	18.23	<0.0005
Other symptoms																	
<55 yr	8	3	7	3	7	7	15	7	2	0	2	3	64	22.6	<0.01	[a]	[a]
55+ yr	5	3	1	9	1	4	4	5	1	0	0	2	35				
All ages	13	6	8	12	8	11	19	12	3	0	2	5	99	28.10	<0.005	[a]	[a]

[a] Roger's test is not appropriate (18).

seasonal patterns were confirmed [($\chi^2_{GF} = 6.89$; $p > 0.60$) ($R = 12.82$; $p < 0.0001$)] in the younger age group, with no significant trend in the older group ($\chi^2_{GF} = 18.66$; $p < 0.05$). This latter series does not show any seasonal difference even when analyzed by quarters ($\chi^2_3 = 4.52$; $p > 0.30$).

Analysis by ethnic distribution for patients under age 55 presenting with a lump (Chart 3) shows that Roger's test can be applied to all 3 main ethnic groups and that the trend is statistically significant for both the Asian-African ($R = 6.58$; $p < 0.05$) and European-born patients ($R = 8.98$; $p < 0.025$). For the small group of Israeli-born patients, the value of R is not statistically significant ($R = 2.69$; $p > 0.20$). Nevertheless, almost one-half of the 78 cases are the first presented in the 4-month period of April through July. Thus, the strong seasonality pattern is implied for each of the ethnic groups.

Further analysis by extent of tumor at diagnosis (Chart 4) indicated that the uneven monthly distribution of the under-55 age group cases is almost exclusively limited to those presenting with nonlocalized disease, with 33% of the women presenting in the months of April through June. In contrast, women with a localized tumor at diagnosis had a fairly even monthly distribution with 25% occurring in the respective period, as expected. In the month of June alone one can note 13.7% of

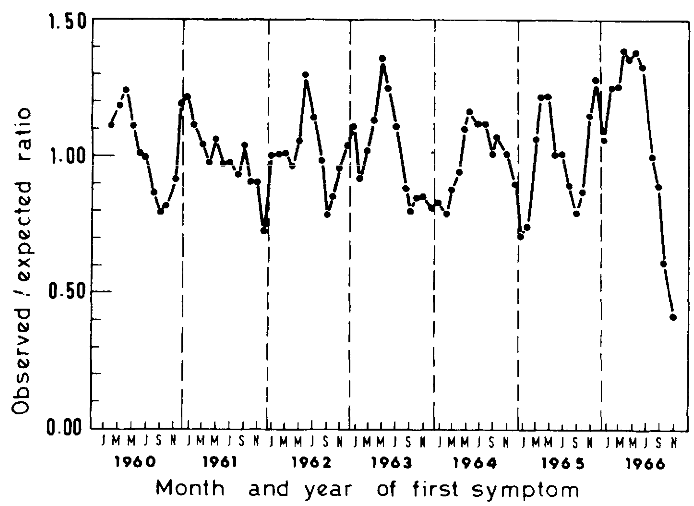

Chart 2. Frequency distribution of cases under 55 years of age by month (*abscissa letters*) and year of self-detection; 3-month moving averages.

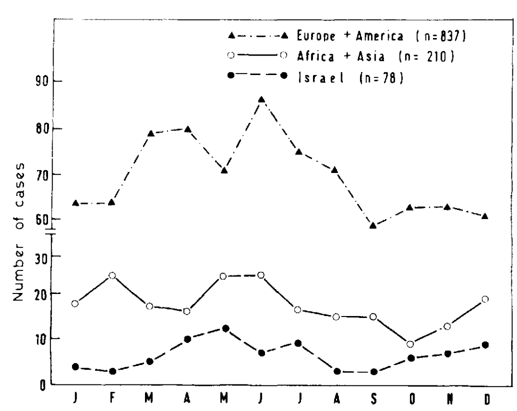

Chart 3. Frequency distribution of cases under 55 years of age by month (*abscissa letters*) and ethnic group.

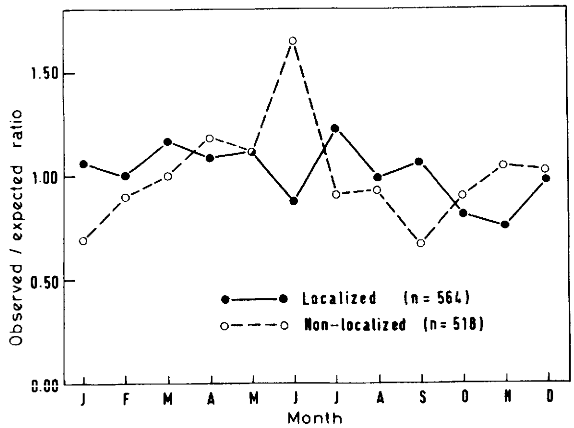

Chart 4. Frequency distribution of cases under 55 years of age by month (*abscissa letters*) of first symptom according to tumor extent at diagnosis.

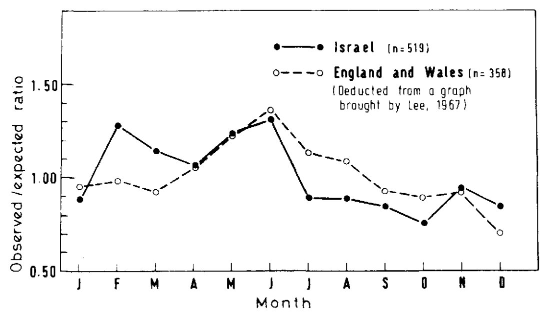

Chart 5. Comparison of the frequency distribution of first symptomatology of breast cancer in women under age 45. *Abscissa letters,* month. British data adapted from Lee (15).

the nonlocalized cases as compared to 7.3% of the localized ones. The quarterly differences are statistically significant ($\chi^2_3 = 8.66$; $p < 0.035$) for the nonlocalized series but not significant ($\chi^2_3 = 4.52$; $p > 0.2$) for the localized series.

A similar analysis was performed for patients over the age of 55, but no seasonal patterns were observed.

DISCUSSION

The data show a clear seasonal pattern in symptomatology, primarily for the premenopausal disease category presenting with nonlocalized self-detected tumor.

Detection of first symptoms may be indicative of change in the tumor growth, although the detection itself may reflect nonbiological factors rather than the actual onset of disease. The lag time between the transition from clinical, nondetectable to detectable state may be too long for a reliable association with a specific month. On the other hand, many patients reported no palpation of a mass till a few days before visiting their physician. This group of patients may reflect a rapidly growing tumor (12). Indeed, tumors with enhanced growth may be the ones responsible for the occurrence of the observed pattern in our data.

A similar seasonal pattern regarding the discovery of the first symptom (Chart 5) was observed in Great Britain (15). Indeed, more frequent bathing and lighter clothes may draw a woman's attention to abnormalities in her breasts in the spring. It is therefore plausible to expect that more mammary tumors detected during this period should be found to be in an earlier stage of development than those detected during the rest of the year. However, while localized cases show no clear seasonal pattern, a statistically significant pattern was found in the nonlocalized group. Therefore, our findings suggest a higher propensity of metastases of breast tumors, possibly due to hormonal imbalance, rather than a spurious concentration of cases.

In previous studies (3, 4), one of us postulated that a changing hormonal balance during the year could be reflected in rhythmic variations of several animal and human life functions. The similar annual pregnancy duration found in man and 3 domesticated animal species (3) suggests fundamental factors participating in the causation of these variations. The same holds true for the similarity in seasonal variations of births with congenital dislocation of the hip in various countries (1, 4). Hormonal factors play a role in the time implantation of the fertilized egg as well as in the beginning of parturition.

Marshall and Swan (17) postulated that the varying growth rates of children's stature during the year might constitute a response to an internal cyclic mechanism. Thomas *et al.* (21) and Doyle *et al.* (6) also felt that an inherent biological rhythm was the most likely explanation for the seasonal variation in hormonal-related serum cholesterol concentration (2).

There is also some direct proof of seasonally changing plasma concentrations of various hormones that are assumed to be involved in the pathogenesis of breast cancer. An international geographic chronobiological study conducted by Halberg *et al.* (11) compared the daily fluctuations of prolactin over the year. They found that the amplitude of the daily rhythmic oscillations of plasma prolactin increased in winter and spring as compared with summer and autumn. The fact that this phenomenon was much more pronounced in Japanese than in American women is in line with other indirect evidence of hormonal differential patterns on an ethnic basis in relation to breast cancer etiology (10, 16). In this context, it is of special interest to note that the circannual amplitude of 17-hydroxyprogesterone, estrone, and prolactin described above was found in premenopausal women but decreased subsequently. This observation is consistent with our finding that seasonality is more pronounced in women under age 55.

By the same token, a circannual rhythm was found in the level of estrogen receptors in breast cancer in women, with higher values in late autumn and lower values in the spring (13). As the presence of estrogen receptors may exert a protective action, the changing hormonal balance may be less harmful in autumn than in spring.

Further investigations to elucidate the mechanism of the propensity of cancer may hopefully lead to preventive programs.

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