Seasonal variation in breast cancer incidence. Circumstantial or default event?

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Summary

It has been previously suggested that seasonality in the detection of breast cancer is mostly seen in countries with distinct climatic variations. Patient characteristics and delays have been implicated in the etiology of peak presentation. Seasonality has been more marked in premenopausal women, while delays have been attributed to both patients and health care systems. *Patients:* A total of 1,411 women who presented with breast cancer to our department were analyzed according to their age, menopausal status, site, stage, grade, ER and PR status, c-erb-2 and Ki-67 (412) during the year. *Results:* The seasonal variation was statistically significant, but no statistically significant differences were established between corresponding subgroups. *Conclusion:* The seasonal variation most probably reflects temporal, psychosocial and behavioral patterns in the Greek female population. Since we do not have the ability to recognize the actual onset of any cancer and then correlate it with various different independent factors we can not correlate its influence on survival or biological marker manifestations.

Key words: Seasonal variation; Breast cancer.

Introduction

There are few reports of seasonal variation worldwide in the diagnosis of malignant neoplasms as well as other potentially lethal medical conditions. There are reports on seasonal variation in the diagnosis and reporting of malignant melanomas, lymphomas, leukaemias, breast and childhood cancers. Such variations were first noted in the 1960s and some show intriguing temporal patterns, reflecting on either biological phenomena or administrative differences in the likelihood of tumor detection and registration [1]. Especially for breast cancer there are several retrospective reports that relate, positively or not, to its prognosis with the season of occurrence. It is not remarkable that there are reports which either confirm a positive relationship between seasonal distribution and biological factors as well as prognosis and survival as independent phenomena or totally disagree with evidence based on epidemiological data. When we noticed that this variation might occur in our patients we decided to retrospectively analyze our breast cancer registry to determine whether any seasonal variations exist and to correlate the seasonal incidence of breast cancer with the most known independent factors related to its prognosis.

Material and Methods

The study is based on all female breast cancer cases diagnosed and treated in our Breast Unit over a 22-year period between 1988 through 2009. Cases with an unknown month of diagnosis were excluded from the analysis. In total, 1,411 cases were diagnosed with invasive or in situ breast carcinoma. Depending on the data, we separated the patients according to their age (1,374), menopausal status (1,336), site (1,368), stage (1,128), grade (1,062), ER and PR status (1,374), c-erb-2 (729) and Ki-67 (412) during the year. We noted that during August the cases were eliminated, so it was decided to exclude this particular month to avoid bias of the results. The time of diagnosis was the day of the first presentation of the patient to the Breast Unit and the diagnosis was clinically or histologically confirmed.

Results

Data from each calendar year were standardized to 12 months of equal duration and the month of peak diagnosis was identified thereafter. Percentages were also calculated to achieve comparable monthly results. For statistical analysis the χ^2 test for heterogeneity was used. Statistical significance was determined at the 95% confidence interval (CI).

The distribution of month of cancer detection by patients is shown in Figure 1. There was a significant annual cyclic variation in month of diagnosis with the months of highest detection being early summer and autumn and the month of lowest detection being August following by January and February. As shown in Table 1, the seasonal variation was statistically significant ($p < 0.0001$) at the 95% CI with August not included in the measurement. The χ^2 test was used to detect any deviation from a uniform monthly distribution according to the patient's age, menstrual status, pTNM stage and grade of the tumor, ER and PR status, tumor localization (right or left breast) and the presence of c-erb-2 and ki-67 expression (p = 0.3963, 0.3397, 0.4274, 0.1955, 0.1764, 0.1455, 0.0959, 0.8777 and 0.3013, respectively). No statistically significant differences were established between corre-

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Table 1. — *Statistically significant results in seasonal variation for 1,411 patients.*

Basic Statistical Measures				Chi-Square Test for Equal Proportions*	
Location		Variability			
Mean	6.73	Std deviation	3.36	Chi-square	45.7365
Median	7.00	Variance	11.28	DF	10
Mode	7.00	Range	11.00	*p* value	< .0001
		Interquartile range	6.00		

*August not included.

sponding subgroups. Pre- and postmenopausal women showed a seasonal variation in the presentation of breast malignancy, with both groups peaking in July and the premenopausal group also peaking in October and December. The observed differences were not however statistically significant. The case was similar for the dual peaks seen in the variation of the hormonal status of tumors. A statistically significant trend was observed in cases with positive lymph nodes. Again, bimodal peaks occurred in July and December. They were considered however to be of low magnitude.

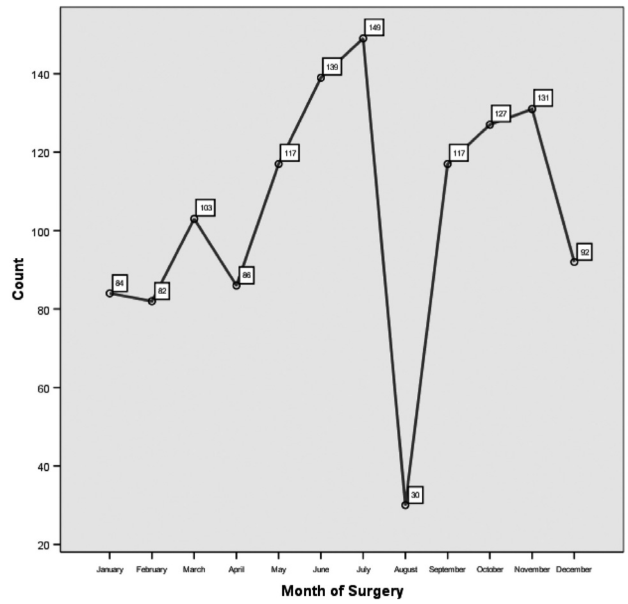

Figure 1. — Number of breast cancer incidents per calendar month.

Discussion

The major problem of all published reports concerning seasonal variation of breast cancer incidence is the fact that we are unable to evaluate the exact time of cancer development; therefore it is difficult to extract safe results or correlate independent factors with cancer occurrence.

It has been previously suggested that seasonality in the detection of breast cancer is mostly seen in countries with distinct climatic variations, with Israel peaking in spring [2], the USA in spring and late fall [3] and Southern England in June [4]. In the southern hemisphere peaks were detected in late spring [5] and early summer [6] in New Zealand, while there are reports of dual peaks occurring in spring and late autumn in the USA and Bulgaria, for self-detected tumors requiring surgery [3, 7]. Galea and Blamey reported no significant variations in the monthly frequencies of breast tumor detection in Nottingham, England [8].

The time between transition from a clinical, non-detectable state to a detectable state may be too long for a reliable association with a specific month. Cohen *et al*. found a clear seasonal pattern in symptomatology especially for premenopausal disease presenting as a self-detected tumor assuming that the detection of symptoms indicates a change in tumor growth rather than actual onset of the disease [2]. On the other hand, Mason *et al*. showed that the season of tumor detection may influence known factors that predict survival of patients such as ER or PR status and positive axillary lymph nodes [6].

Hormonal variations and tumor-hormone receptor status have, in many cases, been related to the season of detection of breast neoplasms [3]. Melatonin seasonal variation and its effect on ovarian steroidogenesis may play a role in breast tumor pathology and time of presentation. Melatonin inhibits proliferation of estrogen-responsive breast cancer cell lines and its levels are higher in the winter. Vizula *et al*. reported an increased frequency of both positive estrogen and progesterone receptors in the autumn months in premenopausal women and a decrease in the spring months [9]. On the other hand, in postmenopausal women positive receptor status peaked in the summer months and was negative in the late winter months.

Despite these results the cause of the relationship between season of detection and survival remains uncertain. Although some of the hypotheses are intriguing, our results do not establish a statistically significant relationship between oestrogen and progesterone receptor status and seasonality. However, it might be worth looking into the relationship between survival rates and time of tumor detection, as previous studies suggest that the time of the first detection relates significantly to the later behavior of the tumor, and may reflect seasonal changes in hormone dependent growth [6].

Comparable results concerning cancer survival and the season of diagnosis were found by Lim *et al*. who tried to correlate both season of diagnosis and sunlight exposure with cancer survival with limited influence of the latter [10], and by Roychoudhuri *et al*. who found that diagnosis in the summer is associated with substantially decreased mortality among women with breast cancer without it being able to indicate a specific factor that may influence these results [11]. On the contrary, Galea and Blamey, reported no relationship either for frequency of tumor detection and seasonal pattern, or season of detection and survival [8]. As shown in our results from a statistically strong number of cases in our country, even though we have a totally different climate compared with Sweden, we are closest to Lambe *et al.'s* results – not in terms of equivalent month distribution, but in the assumption of social factors that may influence the breast cancer seasonal variation rather than the biological matters. Previous reports on the seasonal variation in breast cancer diagnosis in Greece demonstrate dual peaks in spring and autumn [12]. In contrast to this study, we have shown the highest frequency distributions of breast cancer diagnosis in early summer and the beginning of winter.

The seasonal variation most probably reflects temporal, psychosocial and behavioral patterns in the Greek female population. During the summer months women change into lighter clothing and tend to be more observant about any changes in their body. Most women likely perform breast self-examination (BSE) and visit their physician prior to their holidays. As the majority of Greeks take their holiday in August, the low frequency distribution in this month, together with the peak in July could reflect behavioral characteristics in self-referral, rather than an etiological determinant in breast malignancy presentation. In addition, the reduced diagnostic capacity and evaluation of patients with suspected breast cancers in August could also contribute to the low frequency numbers observed. Similarly, the early winter peak could be attributed to the upcoming Christmas holiday and could represent another female internal reminder to perform a BSE, as has been previously pointed out by Ross *et al*. [3].

In conclusion, this study contributes to the overall understanding of breast cancer epidemiology in Greece and adds to the existing knowledge on seasonal variation in malignant breast tumor detection. It would be of great interest if we had the possibility in the future to substantially recognize the actual onset of any cancer and then correlate it with various different independent factors that may influence survival or biological marker manifestations.

References

[1] Lambe M., Blomqvist P., Bellocco R.: "Seasonal variation in the diagnosis of cancer: a study on the national cancer registration in Sweden". *Br. J. Cancer*, 2003, *88*, 1358.

[2] Cohen P., Wax Y., Modan N.: "Seasonality in the occurrence of breast cancer". *Cancer Res*., 1983, *43*, 892.

[3] Ross J.A., Severson R.K., Davis S., Stanford J.L., Potter J.D.: "Seasonal trends in the self-detection of breast cancer: indications from the Cancer and Steroid Hormone (CASH) study". *Breast. Cancer Res. Treat*., 1997, *42*, 187.

[4] Kirkham N., Machin D., Cotton D.W., Pike J.M.: "Seasonality and breast cancer". *Eur. J. Surg. Oncol*., 1985, *11*, 143.

[5] McIntyre H., Blue J., Harman J.: "A seasonal variation in breast cancer". *N. Z. Med. J*., 2002, *115*, U45.

[6] Mason B.H., Holdaway I.M., Stewart A.W., Neave L.M., Kay R.G.: "Season of initial discovery of tumour as an independent variable predicting survival of breast cancer". *Br. J. Cancer*, 1990, *61*, 137.

[7] Dimitrov B.D., Shangova-Grigoriadi S., Grigoriadis E.D.: "Cyclicity in variations of incidence rates for breast cancer in different countries". *Folia Med. (Plovdiv)*, 1998, *40* (3B suppl.), 66.

[8] Galea M.H., Blamey R.W.: "Season of initial detection of breast cancer". *Br. J. Cancer*, 1991, *63*, 157.

[9] Vizula R., Zaloudik J., Dusek L., Vermousek I.: "Seasonal variation in estrogen and progesterone receptor levels in breast cancer-a factor in data interpretation". *Neoplasma*, 2001, *48*, 19.

[10] Lim H.S., Roychoudhuri R., Peto J., Schwartz G., Baade P., Moller H.: "Cancer survival is dependent on season of diagnosis and sunlight exposure". *Int. J. Cancer*, 2006, *119*, 1530.

[11] Roychoudhuri R., Robinson D., Coupland V., Holmberg L., Moller H.: "Season of cancer diagnosis exerts distinct effects upon short- and long-term survival". *Int. J. Cancer*, 2009, *124*, 2436.

[12] Vassilaros S., Tsiliakos S., Adamopoulos D., Papadiantis J., Varveris H., Sakelaris J. *et al*.: "Seasonal variations in the frequency distribution of breast cancer in Greek women according to the month of their birth". *J. Cancer Res. Clin. Oncol*., 1985, *110*, 79.

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