

## Seasonal Variation in Inflammatory Breast Cancer

Research Article

Levine PH<sup>1</sup>, Liu Y<sup>2</sup>, Veneroso C<sup>2</sup>, Hashmi S<sup>2</sup>, Cristofanilli M<sup>3</sup>

<sup>1</sup>University of Nebraska Medical Center, Nebraska Medical Center, Omaha, USA.

<sup>2</sup>The George Washington University, School of Public Health and Health Sciences, USA.

<sup>3</sup>The Lurie Cancer Center, Northwestern University, Chicago, USA.

### Abstract

**Purpose:** The epidemiologic characteristics of inflammatory breast cancer (IBC) suggest a strong environmental influence. Preliminary data from cluster studies have suggested that IBC may be precipitated by infectious agents or exposures to various chemicals. To investigate the infectious agent hypothesis we looked for seasonal variation in onset of IBC.

**Methods:** We compared the IBC incidences in Canada and the states in the United States with cold winter temperatures to IBC incidences in states with milder winter temperatures. The IBC cases were characterized by the state they lived in and season, when diagnosed.

**Results:** Of the 306 IBC cases that were evaluable, the average number of cases per month in the winter was 20.3, compared to 27.2 diagnosed in the rest of the year. Of the 203 cases in the cold winter group, the average number in winter months was 13 vs. 18.2 for the non-winter months. In the other group of 103 patients, the average number in winter was 7.3 vs. 9 in the non-winter months. The percentage of cases diagnosed in winter in the cold winter group was lower than in the high winter group.

### Introduction

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer with unknown etiology and generally poor outcome. It is characterized by rapid onset with diffuse edema (peau d'orange) and redness (erythema). Several studies have implicated a mouse mammary tumor virus (MMTV) - like virus, also called human mammary tumor virus (HMTV) [1] as a possible etiologic agent in breast cancer [2-4] and we have observed increased expression of this suspected virus in IBC [5]. The aggressiveness of this form of breast cancer increases the opportunity to investigate environmental triggers since the latent period is likely to be much shorter than that for non-inflammatory breast cancer, which can be decades in becoming clinically apparent [6]. Several reports suggesting important environmental contributions include a Tunisian study showing that women with breast cancer living in rural areas have a much higher risk of developing the inflammatory form of breast cancer than women living in urban areas [7], the decrease in incidence in Tunisia over decades attributed to improving socioeconomic status [8, 9],

and the observation of time-space clusters of IBC [10, 11]. A particularly striking finding is the clustering of IBC, which we reported in a California workplace [10], but other clusters have also been observed [11]. North Africa has been reported to have a higher incidence of IBC than other parts of the world [12, 13] and this observation has correlated with the finding of viral antigens and sequences supporting the role of the MMTV - like virus in Tunisian breast tumors more frequently than in tumors from breast cancer patients in other parts of the world [5, 14]. The apparently more important impact of environmental factors on IBC etiology is compatible with a recent study suggesting that genetics play less of a role in IBC than in non-inflammatory breast cancer [15].

Mouse MMTV is primarily transmitted through breast milk [16] and recent studies indicate that this is a likely route for HMTV transmission as well [17]. Since this mode of transmissions seems to preclude HMTV as being responsible for clustering, we decided to look for evidence of other infectious agents in triggering IBC by examining the seasonality of onset of symptoms and diagnosis in this disease.

#### \*Corresponding Author:

Paul H. Levine MD,  
University of Nebraska Medical Center, 984395 Nebraska Medical Center, Omaha, NE 68198-4395, USA.  
Tel: 402-559-4248  
Fax: 708-778-8739  
E-mail: paulhlevine@earthlink.net

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## Materials and Methods

### Study population

The study population of 324 IBC patients consists of two groups of IBC patients referred from 2002 to 2012, both of which have patients from the US and Canada.

The first referral group consisted of 161 patients reported to the IBC registry (IBCR) established at the George Washington University. All patients were interviewed by one of us (PHL) and a detailed clinical history was obtained focusing on the onset of symptoms and date of diagnosis. Medical records, pathology reports, diagnostic tests and laboratory results were obtained from private physicians and hospitals.

The second referral group consisted of a 163 patients treated at the Fox Chase Cancer Center (FCCC) and Thomas Jefferson University (TJU). All of these patients were interviewed by one of us (MC), and at the time of the initial visit a detailed series of questions were specifically directed at identifying the accurate time of the first onset of symptoms/signs, including skin rash, swelling, pain, nipple retraction and palpable mass. Patients were also asked about any imaging studies and other interventions following the described episodes. Patients with newly diagnosed disease completed diagnostic work-up (e.g. breast and/or skin biopsy) and staging. Moreover, all other cases with previous documented histological diagnosis underwent review of pathology and imaging for confirmation of IBC.

The criteria for the diagnosis of IBC was based on the consensus case definition developed by a panel of experts focusing on redness, warmth and edema of acute onset occurring within six months and associated with a pathological diagnosis of cancer [18]. In all 324 cases the time of disease onset preceded the time of confirmed diagnosis (diagnostic biopsy) by less than six months. All the cases were clinically and/or pathologically verified. Informed consent was obtained from all patients in the study.

Of the 324 patients, eighteen patients were excluded from the study: eight patients with secondary IBC (occurring at the surgical site of a previously treated non-IBC cancer) and ten with duplicate or missing values on residency or the time of first onset of symptoms/signs and diagnosis.

The aim of this study was to investigate seasonal variation in cancer incidence in IBC patients. In this study we compared the IBC clinical onsets and dates of diagnosis in Canada and the states in the United States that have cold temperatures in the winter and milder and/or hot temperatures in the rest of the seasons (Group 1) with the IBC clinical onsets and dates of diagnosis in the states that have milder temperatures in the winter and less variation in temperatures among the seasons (Group 2).

The IBC cases were categorized by the state in which they lived when diagnosed and the season in which they were diagnosed. The seasons, defined by the National Oceanic and Atmospheric Administration (NOAA) are spring (March through May); summer (June through August); autumn (September through November),

and winter (December through February).

The group with the cold winters (Group 1) was defined as all states whose average monthly temperature is below 35 degrees Fahrenheit (F) for the winter months (Dec., Jan. Feb.). Group 1 group consists of Canada and 32 states (Alaska, Colorado, Connecticut, Idaho, Illinois, Indiana, Iowa, Kansas, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New York, North Dakota, Ohio, Oregon, Pennsylvania, Rhode Island, South Dakota, Utah, Vermont, Washington, West Virginia, Wisconsin, Wyoming). Group 2 consists of the rest of the states and the District of Columbia.

The monthly temperatures for each state was taken from the NOAA National Climatic Data Center of the United States. <http://www.currentresults.com/Weather/US/average-state-temperatures-in-winter.php>, <http://www.erh.noaa.gov/lwx/climate/dca/dcatemps.txt>. The temperatures are based on data collected by weather stations throughout each state during the years 1971 to 2000.

### Analytical Methods

We used the month of diagnosis rather than the date of clinical onset because of its more objective nature and our observation that the vast majority of patients had less than a month between first symptoms to diagnosis [19]. Using the month of diagnosis, we calculated the number of IBC cases by season and by geographical group. We then compared the number of incident cases by season within each Group and compared the variation among the seasons between the two geographical groups (see Table 1 and Figure 1). Because in both groups the variation among the spring, summer, and autumn seasons was very little, we calculated the average monthly number of cases for spring, summer and autumn combined and compared that with the average monthly number of cases with winter (see Table 1).

## Results

### Patient Population

Three hundred and six women with known geographic location and date of diagnosis between 2002 and 2012 were evaluated. Of the 223 women with known race and ethnicity, 206 (92%) patients were non-Hispanic white, 13 (5.83%) were Asian, three (1.35%) were Hispanics, and one was black (0.45%). Of the 203 patients with a known age, the age of diagnosis was 30-82 with a median age of 49.

### Seasonal and Geographical Patterns

Group 1 (cold winters) had 203 IBC cases (66.3%). Group 2 (mild winters) had 103 IBC cases (33.7%).

In our first analysis, we reported the average number of IBC cases per month diagnosed in the winter (20.3), and compared that with the average monthly number of IBC cases diagnosed in the rest of the seasons (27.2) for all of our IBC cases. We performed the same analysis separately for Group 1 and Group 2 (both on Table 1). While the average monthly number of IBC cases is lower for

both groups between winter and the rest of the seasons, this is more pronounced in Group 1. In Group 1 where they have cold winters, the average monthly numbers of IBC cases in winter is 13 compared to 18.2 in the rest of the seasons. In Group 2 (mild winters), the average monthly number in winter is 7.3 compared to 9 in the rest of the seasons.

Next we determined the variation of IBC cases among the seasons for each Group. For Group 1 (cold winters), there was a prominent variation in the incident cases of IBC between winter and the other seasons, with only 39 cases in the winter vs. 58 cases in the spring, 54 in the summer, and 52 in the autumn. For Group 2 (mild winters), there was little variation in the number of IBC cases among the seasons with 22 cases in the winter, 28 in the spring, 27 in the summer and 26 in the autumn (Table 2). A comparison of total percentages in Group 1 (cold winters) and Group 2 (mild winters) shows a lower percentage of winter IBC

cases appearing in the group with cold winters.

### Discussion

Seasonality of IBC was observed in the patients in Group 1 (cold winters) to a greater extent than in patients in Group 2 (mild winters). Group 1 has more variation in the temperatures in the seasons and has on average, freezing and below freezing temperatures, as compared to Group 2. Group 1 has fewer IBC cases in the winter as compared to the rest of the seasons whereas Group 2 has almost the same number of IBC cases in each season. The percentage of winter onset IBC is lower in Group 1 (cold winters) than in Group 2 (mild winters). The seasonal variation in areas with cold winters is highly suggestive of an infectious trigger.

**Table 1. Average number of IBC cases by month in winter compared to the rest of the seasons combined and by geographical Group.**

Seasons	Total (N=306)	Group 1 (N = 203)	Group 2 (N=103)
Spring - Summer - Autumn	27.2	18.2	9
Winter	20.3	13	7.3

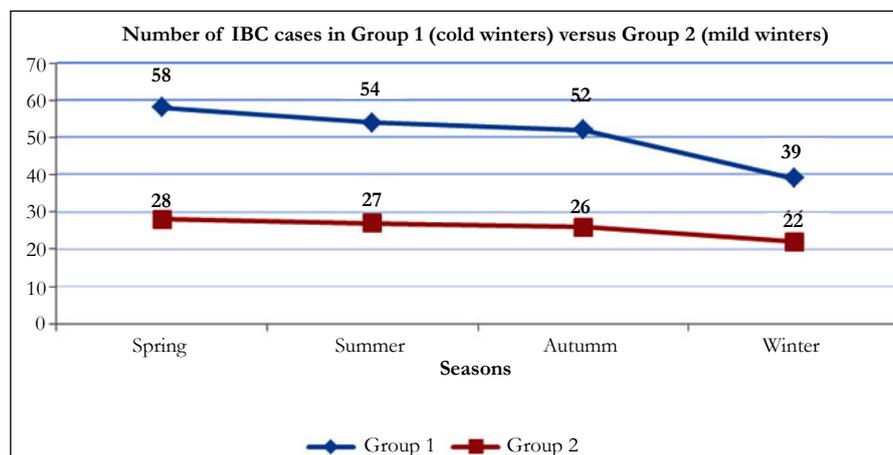
**Table 2. Numbers of persons diagnosed with IBC by season and geographic location.**

Seasons	Group 1 (cold winters) (N = 203)	Group 2 (mild winters) (N=103)
Spring	58 28.6%	28 27.2%
Summer	54 26.6%	27 26.2%
Fall	52 25.6%	26 25.2%
Winter	39 19.2%	22 21.4%

**Table 3. Numbers of persons diagnosed with IBC by winter vs other seasons and geographic location.**

Seasons	Group 1 (cold winters) (N = 203)	Group 2 (mild winters) (N=103)
Non - winter seasons	164 80.8%	28 78.6%
Winter	39 19.2%	22 21.4%

**Figure 1. Number of IBC cases in Group 1 (Cold winters) versus Group 2 (Mild winters).**



Infectious agents play a major role in cancer etiology, more than 16.1% of cancer cases worldwide being attributed to various infectious agents [20]. Seasonal trends in months of diagnosis and/or certain times of year have been reported in some cancers, such as, childhood acute lymphoblastic leukemia [21] and Hodgkin's lymphoma [22]. Burkitt's lymphoma (BL) is another malignancy that has been reported to cluster and has been linked to infectious agents [23]. BL has been reported to have a seasonal variation attributed to malaria seasonality [24].

The seasonal pattern for IBC is consistent with an infectious trigger. The mechanisms of infectious agents causing cancer vary. Some agents cause cancer by transforming cells which proliferate, carrying evidence of the virus in each tumor cell, such as Epstein Barr virus (EBV), hepatitis B virus (HBV), and human T-cell lymphotropic virus-I (HTLV-I). Others cause cancer indirectly through chronic inflammation starting the process towards cancer, such as *Helicobacter Pylori*, hepatitis C virus (HCV) and schistosomiasis haematobium, the resulting malignancy having no footprint of the triggering agent. In most cases, there is a long latent period as noted for HBV and HTLV-I, where infection within the first year of life is the greatest risk factor for developing cancer but the tumor doesn't usually appear for at least 40 years [25, 26]. A viral etiology for human breast cancer has been suggested [5, 14, 1, 3, 4, 27] but a specific human breast cancer oncogenic virus has not been widely accepted.

Since the leading candidate for a human breast cancer virus is biologically and epidemiologically compared to the mouse mammary tumor virus, which is transmitted by milk [16] and is not readily spread in other ways [28], our hypothesis is that another infectious agent is the trigger for the clusters. Our hypothesis is based on our studies of clusters in chronic fatigue syndrome (CFS) where the major manifestations appear to be due to Epstein-Barr virus, an endemic virus where most individuals are antibody positive by age 10 but the disease can be triggered by different agents. In the case of CFS, the predisposing risk factor for a community infection is postulated to be a predisposition to autoimmune disease. For IBC, the risk factors could include the suspected mouse mammary tumor like virus as well as those described elsewhere, such as obesity and early age at first pregnancy [29, 30].

Epidemiologic studies of IBC have particular advantages because of the rapid growth after initiation, unlike non-IBC breast cancer where the disease becomes apparent decades after the inciting carcinogen [6] and the slow growth does not allow pinpointing when the tumor growth actually started. For IBC, the onset is much more sharply defined because by definition the disease has to be rapidly growing with less than a six month diagnostic period from onset of symptoms [18] and clinical observations indicate the rapid appearance in less than a week (MC and PHL personal communication). Thus far, the description of clusters of IBC have suggested chemical or other non-infectious exposures as well as infectious agents [10, 11] but this analysis strongly supports the likelihood that infectious agents do play an important role in certain geographic regions. It is important to note that for virtually all oncogenic infectious agents, the cancer only occurs in a small percentage of infected individuals and therefore the focus has to be on the susceptibility factors that make some individuals more prone to develop malignancy rather than either asymptomatic infection or a non-malignant disease. Another possibility to

consider is that the triggering agent may not be the same for all outbreaks, such as indicated by current evidence implicating different triggers for chronic fatigue syndrome (CFS) [31] which has been linked to the subsequent occurrence of non-Hodgkin's lymphoma (NHL) [32, 33]. The virus most closely linked to NHL is EBV, which is apparently reactivated in CFS [34], but as noted CFS has many infectious triggers [31] and EBV is unlikely to cause clusters since more than 90% of healthy individuals are immune to infection by age 20. However, as with other illnesses, similar clinical features may appear triggered by different infectious agents. For example, infectious mononucleosis can be caused by Epstein-Barr virus, cytomegalovirus or human herpesvirus-6.

While our data show a seasonality in the diagnosis of IBC, the trend we have observed needs to be confirmed with additional cases.

Current laboratory techniques should provide further understanding of the possible contribution of infection to IBC, either through molecular examination of tumors for viral or bacterial agents or by studying antibody patterns in outbreaks. The data on infectious agents thus far are limited. Besides the studies on the mammary tumor virus like agent, which is suspected as being passed through breast feeding [35, 36, 17] and like EBV is unlikely to cause outbreaks of IBC, other agents have only been reported sporadically [37]. Studies are now in progress to examine tumors from IBC clusters for infectious and non-infectious carcinogens and hopefully will result in new relevant information on the etiology of IBC.

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