

# Factors Affecting Rise in the Incidence of Infiltrating Lobular Carcinoma of the Breast

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**ABSTRACT:** **Background:** Infiltrating ductal carcinoma and infiltrating lobular carcinoma account for more than 90% of all invasive breast cancer histological types. The rate of ILC is reported to be increasing steadily in the United States and Europe.

**Objectives:** To describe the trend in the incidence of ILC in a large cohort of patients who underwent surgery in a single institution over an 18 year period.

**Methods:** Our comprehensive database of 2175 consecutive patients with invasive breast cancer diagnosed during the period 1992–2009 served for the analysis. Several potential factors associated with lobular carcinoma as compared with ductal carcinoma were evaluated.

**Results:** During this period, a 2.4-fold increase in the incidence of pure ILC was noted, from 4.6% in the years 1992–1994 to 10.9% in 2004–2006, followed by a modest decrease to 8.7% in 2007–2009. A significant association of lobular malignancies with external hormonal use was noted, including hormone replacement therapy exposure in patients diagnosed at age 50–64, and ovarian overstimulation during in vitro fertilization in those diagnosed at age 50 or less.

**Conclusions:** Better diagnostic tools – such as the liberal use of ultrasound and magnetic resonance imaging – and more accurate pathological definition for ILC type appear to influence the changes in the incidence of ILC in the subgroups of invasive breast cancer.

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**KEY WORDS:** breast cancer, hormone replacement therapy, in vitro fertilization, lobular carcinoma of the breast

Infiltrating ductal carcinoma and infiltrating lobular carcinoma account for more than 90% of all invasive breast cancer histological types, but while the reported incidence of IDC in the United States remained more or less constant during the 13 year period 1987–1999, the rate of ILC has been increasing steadily over the years. As a result, the proportion of

ILC = infiltrating lobular carcinoma  
IDC = infiltrating ductal carcinoma

breast cancer patients with a lobular component has increased from 10% to as high as 16% [1]. A report from Switzerland has shown a 1.2% mean annual increase in the incidence of IDC during the period 1976–99 as compared to a mean annual increase of 14.4% in the incidence of ILC [2].

In a cohort of 2175 patients treated at our center during an 18 year period, we also noted a steady increase in the rate of ILC, but with stabilization and a modest decrease during the last 3 years. The current study presents our data.

## PATIENTS AND METHODS

This was a retrospective study based on accumulated data collected during the 18 year period 1992–2009. All patient charts were reviewed, creating a computerized database. Eighty-two different parameters (including demographics, pathology results, treatment details, hormone replacement therapy and in vitro fertilization) were retrieved and entered into the database by one of the authors (B.C.). The study period was divided empirically into six equal periods, 1992–94, 1995–97, 1998–2000, 2001–3, 2004–6 and 2007–9. Only primary breast cancer was considered in our analysis. Cases of metachronous or recurrent cancer were not included.

Of the 2175 patients, 188 (8.6%) were diagnosed with pure ILC and 58 with mixed ILC and IDC, reaching a total of 246/2175 women (11.3%) who had breast cancer with an infiltrating lobular pattern component. Full data regarding the use of HRT or IVF were available for only 148 of the 246 patients with ILC pathology and these patients served as the basis for our study.

A comparative analysis of hormonal exposure (HRT or IVF treatment) was performed between the 148 patients with ILC pattern (115 pure ILC and 33 with mixed ILC-IDC features) and a randomly selected group of 982 patients with pure IDC. The effect of HRT and IVF on the incidence of ILC was examined in three age groups: < 50 years old, 50–64 years and > 65.

HRT = hormone replacement therapy  
IVF = in vitro fertilization

**Table 1.** Histological types of female invasive breast cancer (n)

Histological type	1992–94	1995–97	1998–2000	2001–3	2004–6	2007–9 (n)	Total (n)
Infiltrating ductal carcinoma	132	204	247	357	393	460	1793
Infiltrating lobular carcinoma	7	11	20	49	53	48	188
Mixed infiltrating lobular and ductal carcinoma	4	5	18	13	8	10	58
Others	10	15	11	35	32	33	136
Total invasive breast cancer	153	235	296	454	486	551	2175

### STATISTICAL ANALYSIS

Statistical tests were performed against two-sided alternatives using the SPSS-15 computer program. A level of  $P < 0.05$  was used to determine statistical significance.

## RESULTS

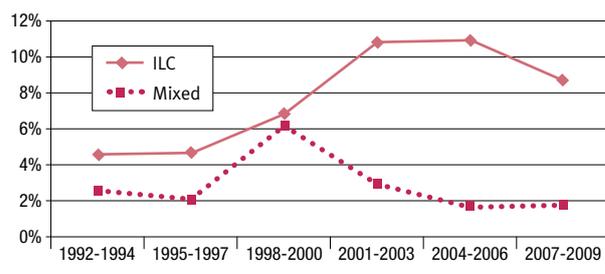
### CHANGES IN THE INCIDENCE OF ILC OVER THE YEARS

Table 1 shows the distribution of the various pathological types of invasive breast cancer diagnosed and treated during the study period. It becomes evident that the relative incidence of ILC increased from 4.6% during the period 1992–94 to 10.8–10.9% during the period 2001–3 and 2004–6, accounting for an almost 2.5-fold change in the rate of ILC, followed by a modest decrease in the rate to 8.7% during the period 2007–9. Figure 1 demonstrates these changes graphically.

### HRT, IVF AND ILC

In the age group 50–64 years, 17 of 60 patients (28.3%) with ILC pattern were treated with HRT as compared to 52 of the 397 women (13.1%) with IDC in the same age group. This difference is statistically significant ( $P = 0.006$ ) [Table 2].

Four of the 148 patients with ILC underwent IVF treatment cycles as compared to only 3 of 982 patients with IDC. With regard to the age group younger than 50 years at diagnosis of breast cancer, 8.1% of patients with ILC pattern had a history of previous IVF treatment as compared to only 0.4% for the IDC group of patients ( $P = 0.007$ ) [Table 3].

**Figure 1.** Changes in the incidence of ILC and mixed ILC and IDC during the years 1992–2009**Table 2.** Association of HRT use and pure ILC, mixed infiltrating and ductal carcinoma and pure IDC (n)

Age (yrs)	ILC	Mixed ILC and IDC	IDC	P value*
< 50	0/24 (0%)	0/13 (0%)	8/248 (3.2%)	0.602
50–64	11/48 (22.9%)	6/12 (50.0%)	52/397 (13.1%)	0.006
≥ 65	1/43 (2.3%)	0/8 (0%)	6/337 (1.8%)	1.0

\*Comparison of pure ILC and mixed ILC and IDC versus pure IDC

**Table 3.** Association of IVF treatment and pure ILC, mixed infiltrating lobular and ductal carcinoma, and pure IDC (n)

Age (yrs)	ILC	Mixed ILC and IDC	IDC	P value*
< 50	2/24 (8.3%)	1/13 (7.7%)	1/248 (0.4%)	0.007
50–64	1/48 (2.1%)	0/12 (0%)	2/397 (0.5%)	0.345
≥ 65	0/43 (0%)	0/8 (0%)	0/337 (0%)	1.0

\*Comparison of pure ILC and mixed ILC and IDC versus pure IDC

## DISCUSSION

The incidence of lobular carcinoma of the breast is cited to range between 10 and 15% [1,2]. A review of the older literature on ILC showed an incidence as low as 3–4.2%, but this refers to about 30–40 years ago [3,4]. The observation that the incidence of lobular carcinoma of the breast is increasing is well documented in the modern literature [1,2] and is also shown by our data. However, during the period 2007–9, we documented a modest decrease in the rate of ILC [Table 1].

Although the objective of this paper was to address the changes in the incidence of ILC, additional factors that might contribute to this change should be mentioned. Three main points should be considered when trying to explain the increase in the incidence of ILC: a) increased use of HRT and IVF, b) improved diagnostic tools, and c) more accurate pathological classification or diagnosis.

### HRT AND IVF

Approximately 38% of postmenopausal women in the USA used HRT [5] prior to the publication of the Women's Health Initiative study [6]. Because estrogen alone was found to be

associated with an increased rate of endometrial cancer, the addition of progestins has steadily increased since the mid-1980s [7]. The estrogen/progestin combination is well known for its causal relationship with breast cancer as a whole [6,8], but especially with ILC [9,10]. The publication in 2002 of the Women's Health Initiative study [6] sparked a rapid decline in the purchase of HRT drugs among American women. In Israel, a sharp decline in HRT use was also documented: 20% of women aged 45 years and older purchased estrogen products in 2001, versus 10% in 2007 [11]. As in previous studies [9,10], in our study we documented a statistically significant difference in the history of exposure to HRT in patients with ILC as compared to IDC in the age group 50–64 years. This point is further elucidated in the literature by the molecular level differences between ILC and IDC [12–14], including differences in ER and PR status [14]. While only 81% of IDC patients are ER-positive these figures increase to as high as 92% for ILC. Differences are also noted for PR, it being positive in 60% of patients with IDC and 67% in patients with ILC [14]. Li et al. [9] reported that the use of HRT was associated with an increased rate of ER+/PR+ tumors, but not with an increased rate of ER+/PR- tumors. The decreasing rate of ILC in our series in the last period of the study (2007–9) may be a result of the rapid decline in HRT use [11].

Another statistically significant factor in our study is the different history of IVF treatment in patients with ILC and IDC. To the best of our knowledge, there are no available data on the specific types of breast cancer associated with IVF treatment. The literature is somewhat ambiguous concerning IVF and risk of breast cancer. Keinan-Boker et al. [15], Venn et al. [16], Brinton et al. [17] and Pappo et al. [18] reported an increased risk of breast cancer associated with IVF treatment. However, as previously noted, none of these studies relates to any specific histological type of breast cancer.

## IMAGING

ILC is quite distinct from IDC, appearing clinically as a poorly defined often non-palpable lesion rather than a dominant mass. This causes difficulties in estimating the extent of the disease on physical examination. The same applies when using mammography [19]. Since ultrasound [20,21] and MRI [20,22] are more precise than mammography in detecting and defining ILC, the wider availability of these diagnostic tools might also have contributed to the changes in the detection rate of ILC, translated as increasing incidence. The role of MRI as the best imaging tool for the diagnosis of ILC has now been proved and the Israel Ministry of Health recommends preoperative MRI for any diagnosis of ILC by biopsy.

ER = estrogen  
PR = progestin

## PATHOLOGY

The third issue is the more accurate histopathological diagnosis of recent years, especially since the development of helpful antibodies such as cytokeratins for identifying the more elusive infiltrating lobular carcinoma and E-cadherin. This antibody is demonstrated very weakly in ILC in a perinuclear pattern and not as intensely as the membranous pattern typical of IDC. This pattern of staining expresses the lack of intercellular adhesion, which is the hallmark of invasive lobular carcinomas and the reason for the above described poor circumscription that is so often observed in ILC [23,24].

The prominent decrease in the number of mixed ILC and IDC [Table 1] observed in our series in the years 2001–9 may be explained by the wider use of immunohistochemical markers in the process of histological evaluation.

The literature discussing the increasing incidence of ILC is quite scarce but certainly shows a steady increase over the last decade, although it varies in different articles [1,2]. We noted a 2.4-fold increase in the incidence rate of ILC. The tendency for stabilization and even a decrease in the rate of ILC in recent years documented in our study may be explained primarily by the sharp decline in HRT use [11]. While Li et al. [1] commented that multiple pathologists from many centers participated in their study and therefore the pathological classification might differ among the various groups, in our study the same team of pathologists interpreted the results.

As the current treatment approaches for both types of tumors are similar [25], our observations and those of others regarding the increase in the ILC rate should be directed towards earlier detection of ILC with a more liberal use of techniques such as ultrasound and MRI. More extensive research is needed to define the role of IVF treatment as a possible causative factor of ILC.

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