Increased incidence of lobular breast cancer in women treated with hormone replacement therapy: implications for diagnosis, surgical and medical treatment

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Abstract

A growing body of evidence support the association between the use of hormone replacement therapy (HRT) and a higher risk of both invasive lobular carcinoma (ILC) and invasive ductal–lobular mixed carcinoma (IDLC). Overall biological and clinical features of ILC entail a more cautious diagnostic and therapeutic approach as compared with invasive ductal carcinoma (IDC). ILCs are more frequently multifocal, multicentric and/or bilateral. Mammography and ultrasound show, therefore, significant limitations, while the higher sensitivity of magnetic resonance imaging in the detection of multifocal and/or multicentric lesions seems to improve the accuracy of preoperative staging of ILCs. Early diagnosis is even more challenging because the difficult in the localization and the sparse cellularity of lobular tumours may determine a false negative core biopsy. ILC is characterized by low proliferative activity, C-ErbB-2 negativity, bcl-2 positivity, p53 and VEGF negativity, oestrogen and progesterone positive receptors, low grade and low likelihood of lymphatic-vascular invasion. However, this more favourable biological behaviour does not reflect into a better disease-free and overall survival as compared with IDC. Since lobular histology is associated with a higher risk of positive margins, mastectomy is often preferred to breast conservative surgery. Moreover, only few patients with ILC achieve a pathologic response to preoperative chemotherapy and, therefore, in most patients mastectomy can be regarded as the safer surgical treatment. The preoperative staging and the follow-up of patients with ILC are also complicated by the particular metastatic pattern of such histotype. In fact, metastases are more frequently distributed to the gastrointestinal tract, peritoneum/retroperitoneum and gynaecological organs than in IDC.

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Introduction

Epidemiological data have shown that the incidence rates of lobular breast tumours have increased over the past decades mainly among postmenopausal women, whereas the incidence rates of invasive ductal tumours have remained stable since 1987 (Li et al. 2000a). There is considerable evidence that the use of hormone replacement therapy (HRT) is more strongly associated with the risk of both invasive lobular carcinoma (ILC) and invasive ductal–lobular mixed carcinoma (IDLC) than that of invasive ductal carcinoma (IDC; Li et al. 2000a,b, 2003a,b,c, Chen et al. 2002, Daling et al. 2002, Newcomb et al. 2002, Newcomer et al. 2003, Biglia et al. 2005). These data may have remarkable clinical significance because the use of HRT has increased steadily over the past decades (Hemminki et al. 1988, Wysowski et al. 1995, Wysowski & Governale 2005) until the publication of WHI trial (Rossovou et al. 2002); moreover, ILC and IDC have different clinical behaviours. The aim of this review is to review the biological and clinical features of ILC as compared with IDC and the potential implications for diagnosis, surgical and medical treatment.
Epidemiology

ILC of the breast accounts for 5–15% of all invasive breast malignancies (Fisher et al. 1975). Data from nine cancer registries showed that, whereas the incidence of IDC is stable since 1987, the incidence of ILC and IDLC, a heterogeneous group of tumours made of a mix of lobular and ductal cancer cells, increased 1.52-fold (95% CI, confidence interval 1.42–1.63) and 1.96-fold (95% CI 1.80–2.14) respectively from 1987 through 1999 (Li et al. 2000a, 2003a; Table 1). As a result, the proportion of all breast tumours with a lobular component rose from 9.5% in 1987 to 15.6% in 1999 (Li et al. 2003a). The incidence rates of ILC and IDLC increased mainly in postmenopausal women during 50–59 years of age, although these increases were evident throughout the overall age range (Li et al. 2003a; Table 2). These results are also confirmed by a European population-based study, including 6247 patients with invasive breast tumours recorded between 1976 and 1999 (Li et al. 2003b). ILC incidence was found to rise from 2.9 to 20.5/100,000 with an increase of 14.4% per year, thus showing a disproportionate trend when compared with IDC incidence. This increase affected all age categories and both localized and advanced stages; nevertheless, a statistically significant age-cohort effect was seen since women aged 50–59 years born after 1944 experienced the most marked increase (Li et al. 2003b).

HRT and breast carcinoma

It is generally accepted that the long-term use of HRT increases the risk of developing breast cancer (Rossouw et al. 2002, Beral et al. 2003, Anderson et al. 2004). In the last 10 years several studies have shown a more pronounced negative effect on breast cancer risk of oestrogen plus progestin associations as compared with oestrogen alone (ERT; Colditz et al. 1995, Persson et al. 1996, Colditz & Rosner 1998, Magnusson et al. 2000, Ross et al. 2000, Schairer et al. 2000, Rossouw et al. 2002, Weiss et al. 2002, Beral et al. 2003, Li et al. 2003c, Anderson et al. 2004). Initial data on the oestrogen-alone arm of the WHI trial underlined that the risk of breast cancer for women who were given unopposed oral CEE 0.625 mg daily was not different from that of women who took placebo (relative risk, RR: 0.77; 95% CI, 0.59–1.01; Anderson et al. 2004). More recently, the WHI trial reported that about 7 years of treatment with exogenous oestrogen did not raise the risk of breast cancer in 11 000 women who had previously undergone hysterectomy (Stefanick et al. 2006). The prospective cohort Nurses Health Study observed that the risk of breast cancer positive for oestrogen and progesterone receptors increased only after 15 years of oestrogen treatment, and all breast cancers after 20 years (Chen et al. 2006). Although this studies clarify the risks of oestrogen use, the role of progesterone appear more ambiguous. The higher risk of breast cancer associated with combined HRT suggests that progestin is more important than oestrogen as risk factor for breast cancer development. The WHI trial demonstrated that after a mean follow-up of 5.2 years, women treated with continuous combined HRT had a RR of breast cancer of 1.26 (95% CI, 1.00–1.59; Rossouw et al. 2002). The observational Million Women Study showed a twofold

Table 1 Trends in incidence rates of invasive lobular and ductal breast carcinoma (1987–1999)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total population</th>
<th>IDC</th>
<th>ILC</th>
<th>IDLC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases (age-adjusted incidence rate per 100 000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>6470386</td>
<td>9956 (153.8)</td>
<td>833 (12.9)</td>
<td>442 (6.9)</td>
</tr>
<tr>
<td>1988</td>
<td>6600594</td>
<td>9850 (149.5)</td>
<td>829 (12.5)</td>
<td>503 (7.8)</td>
</tr>
<tr>
<td>1989</td>
<td>6725369</td>
<td>9606 (144.3)</td>
<td>812 (12.0)</td>
<td>454 (6.9)</td>
</tr>
<tr>
<td>1990</td>
<td>6852588</td>
<td>9976 (147.4)</td>
<td>923 (13.5)</td>
<td>483 (7.3)</td>
</tr>
<tr>
<td>1991</td>
<td>6998670</td>
<td>10203 (148.1)</td>
<td>958 (13.8)</td>
<td>598 (8.9)</td>
</tr>
<tr>
<td>1992</td>
<td>7151658</td>
<td>10144 (144.3)</td>
<td>1106 (15.6)</td>
<td>612 (8.8)</td>
</tr>
<tr>
<td>1993</td>
<td>7283478</td>
<td>10150 (141.9)</td>
<td>1037 (14.4)</td>
<td>628 (8.9)</td>
</tr>
<tr>
<td>1994</td>
<td>7408103</td>
<td>10471 (144.4)</td>
<td>1170 (15.9)</td>
<td>640 (8.9)</td>
</tr>
<tr>
<td>1995</td>
<td>7524437</td>
<td>10814 (146.6)</td>
<td>1189 (16.0)</td>
<td>722 (9.9)</td>
</tr>
<tr>
<td>1996</td>
<td>7632458</td>
<td>11219 (150.0)</td>
<td>1253 (16.6)</td>
<td>737 (9.9)</td>
</tr>
<tr>
<td>1997</td>
<td>7732719</td>
<td>11795 (154.5)</td>
<td>1403 (18.2)</td>
<td>870 (11.5)</td>
</tr>
<tr>
<td>1998</td>
<td>7819324</td>
<td>12217 (157.3)</td>
<td>1459 (18.7)</td>
<td>1047 (13.5)</td>
</tr>
<tr>
<td>1999</td>
<td>7893363</td>
<td>12224 (155.3)</td>
<td>1514 (19.1)</td>
<td>1124 (14.3)</td>
</tr>
</tbody>
</table>

Proportional change (95% confidence interval) 1.03 (0.99–1.06) 1.52 (1.42–1.63) 1.96 (1.80–2.14)

IDC, invasive lobular carcinoma; ILC, invasive lobular carcinoma; IDLC, invasive ductal–lobular mixed carcinoma (modified from Li et al. 2003a).

* Rates age adjusted to the 2000 US standard. Because the rates are age adjusted, they do not reflect absolute numbers.
Table 2 Age-specific risk of breast carcinoma according to different histological types (1987–1999)

<table>
<thead>
<tr>
<th>Age</th>
<th>IDC (CI 95%)</th>
<th>ILC (CI 95%)</th>
<th>IDLC (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39 years</td>
<td>1.09 (1.01–1.17)</td>
<td>1.32 (0.92–1.88)</td>
<td>1.52 (1.10–2.11)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>1.01 (0.95–1.08)</td>
<td>1.20 (1.01–1.40)</td>
<td>1.39 (1.17–1.66)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>1.26 (1.18–1.34)</td>
<td>1.76 (1.51–2.05)</td>
<td>2.75 (2.28–3.32)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>0.97 (0.90–1.04)</td>
<td>1.45 (1.24–1.70)</td>
<td>2.11 (1.75–2.55)</td>
</tr>
<tr>
<td>70–79 years</td>
<td>0.94 (0.87–1.01)</td>
<td>1.59 (1.37–1.84)</td>
<td>1.98 (1.66–2.38)</td>
</tr>
<tr>
<td>≥ 80 years</td>
<td>0.86 (0.80–0.94)</td>
<td>1.68 (1.43–1.98)</td>
<td>1.96 (1.56–2.47)</td>
</tr>
</tbody>
</table>

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IDLC, invasive ductal–lobular mixed carcinoma.

IC 95%, 95% confidence interval (modified from Li et al. 2003a).

increased risk of breast cancer for oestrogen–progesterone compounds (RR: 2.00, 95% CI 1.88–2.12; P < 0.0001) and a RR of 1.30 (95% CI 1.21–1.40; P < 0.0001) for oestrogen alone, without any significant differences associated with specific types of oestrogen and progesterin or their doses (Beral et al. 2003). A case–control study performed on 1897 cases and 1637 controls showed that breast cancer risk was higher for those women who were taking sequential combined HRT (Ottawa region, OR 1.38, 95% CI, 1.13–1.68) as compared with those who were taking continuous combined HRT (OR: 1.09, 95% CI, 0.88–1.35), though it did not reach statistical significance (Ross et al. 2000). These data were in contrast with those of a Swedish cohort study where continuous combined HRT was associated with a higher risk than sequential HRT (Magnusson et al. 2000). The hypothesis that the use of progestin carries an additional breast cancer risk as compared with oestrogen alone is also supported by the evidence that progestin increases mammographic density and stimulates proliferation of normal mammary gland (Greendale et al. 1999, Hofseth et al. 1999). The study of progesterone receptor knockout mice confirmed that progesterone is essential for pregnancy-associated mammary gland ductal side branching and alveologenesis, and these morphological changes are dependent on progesterone-induced mammary epithelial proliferation. Moreover, recent studies on BRCA1/p53-deficient mice demonstrated that the progesterone-proliferative signal significantly contributes to mammary tumour susceptibility (Ismail et al. 2003, Poole et al. 2006).

The impact of HRT on breast cancer risk seems to be different depending on histological type.

Six recent studies have reported that ever and current use of HRT is associated with a significant increased risk for the development of IDC, but has little impact on the risk of IDC (Li et al. 2000b, 2003c, Chen et al. 2002, Daling et al. 2002, Newcomb et al. 2002, Newcomer et al. 2003; Table 3). The three studies that evaluated duration of use showed that ILC risk increased as duration of HRT use increased (Chen et al. 2002, Daling et al. 2002, Li et al. 2003c). However, some of these reports have been limited by small numbers of women with lobular cancer, and none has been able to assess the possible impact of very long duration HRT (i.e. > 15 years). In a recent analysis of the Million Women Study, the relative risks of invasive breast cancer in current users when compared with never users of HRT varied significantly according to tumour histology. The relative risks in current when compared with never users of HRT were 2.25 (95% CI 2.0–2.52) for lobular and 2.13 (95% CI 1.68–2.70) for mixed ductal–lobular (Reeves et al. 2006). Also in our series the incidence of ILC was significantly higher in HRT ever users (i.e. ≥ 6 months) when compared with never users (Biglia et al. 2005). In two out of the six studies, risk of breast cancer by different regimens (sequential or continuous combined) of HRT use was reported (Chen et al. 2002, Daling et al. 2002). In one study, it was found that sequential and continuous combined HRT use were both associated with an increased risk of ILC (Chen et al. 2002), while in the other study, only continuous HRT was associated with an increased risk of ILC (Daling et al. 2002). In these studies, the use of ERT was not significantly associated with an increased risk of breast carcinoma for any of the histological groups (Li et al. 2000b, 2003c Chen et al. 2002, Daling et al. 2002, Newcomb et al. 2002, Newcomer et al. 2003). For instance, Li et al. (2003c) have reported that women using ERT, even for 25 years or longer, have no appreciable increase in risk of breast cancer, although the associated odds ratios are not inconsistent with a possible small effect.

It is interesting to notice that the use of HRT has increased in the United States at the same time that the incidence rates of ILC and IDLC have increased (Hemminki et al. 1988, Wysowski et al. 1995, Wysowski & Governale 2005). The number of dispensed outpatient prescriptions for HRT increased...
2.5-fold (153%) from 34.5 million dispensed in 1992 to a peak of 87.3 million in 2000. For July 2002 through June 2003, the year following the publication of the results of the WHI trial, prescriptions for these products declined to 59.6 million, a 32% decrease from their peak in 2000 (Wysowski & Governale 2005).

Lobular cancers

The higher frequency of such histotype when compared with that of the past decades arises relevant diagnostic and therapeutic questions. The peculiar features of ILCs are discussed separately.

Diagnosis of invasive lobular cancer

Standard diagnostic methods such as mammography (Mx) and ultrasound (US) have lower sensitivity for detecting ILC when compared with other invasive breast cancers. This difficulty has been attributed to the specific growth of lobular tumour cells in single rows with a linear fashion around ducts and lobules (targetoid growth; Rosen 2001). This so-called ‘Indian file’ pattern of infiltration causes a modest disruption of the underlying anatomic structures and generates little surrounding desmoplastic stromal reaction (Dixon et al. 1982).

Clinical examination of patients with ILC can be complicated because of vague findings, such as thickening or induration, which are often the only clinical signs, particularly in early disease (Evans et al. 2002).

Mammography

The sensitivity of detecting ILC has been reported to be as low as 57–76% for Mx (Le Gal et al. 1992, Evans et al. 2002), while false negative rates at Mx have been observed to range from 8 to 24% (Helvie et al. 1993, Krecke & Gisvold 1993). In the study by Krecke & Gisvold (1993) the mammograms of patients with ILC initially classified as normal (i.e. false negative) were reviewed after surgery and in almost 50% of the cases the radiologists failed to detect any radiological alteration. Similarly, in a recent analysis, two radiologists retrospectively evaluating preoperative mammograms of 42 ILC found that 35–37% of the cases were under-staged (Veltman et al. 2006). The result of the particular growing pattern of ILC is that a discrete mass with the mammographic appearance of stellate opacity is less common than that

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Ever use</th>
<th>6 months–4.9 years</th>
<th>5–14.9 years</th>
<th>≥ 15 years</th>
<th>Ever use</th>
<th>Past use</th>
<th>Recent use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. (2003c)</td>
<td>1.5 (1.1–2.0)</td>
<td>1.3 (0.8–2.2)</td>
<td>1.5 (1.0–2.3)</td>
<td>1.6 (1.0–2.6)</td>
<td>0.9 (0.6–1.3)</td>
<td>1.6 (0.9–2.8)</td>
<td>1.5 (0.3–7.1)</td>
</tr>
<tr>
<td>Newcomer et al. (2003)</td>
<td>1.1 (0.8–1.5)</td>
<td>1.0 (0.9–2.8)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.2 (0.9–1.6)</td>
<td>0.9 (0.6–1.3)</td>
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</tr>
<tr>
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<td>1.0 (0.8–1.3)</td>
<td>1.0 (0.8–1.4)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.2 (0.9–1.6)</td>
<td>1.0 (0.8–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.2 (0.9–1.6)</td>
</tr>
<tr>
<td>Chen et al. (2002)</td>
<td>1.39 (0.85–2.26)</td>
<td>0.89 (0.50–1.56)</td>
<td>1.49 (0.93–2.39)</td>
<td>0.97 (0.46–2.03)</td>
<td>1.19 (0.58–2.43)</td>
<td>1.43 (1.14–1.79)</td>
<td>1.03 (1.00–1.07)</td>
</tr>
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<td>0.7 (0.5–1.1)</td>
<td>2.6 (1.1–5.8)</td>
<td>1.23 (0.25–5.95)</td>
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IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; OR, odd ratio; CI, confidence interval.

Table 3 Combined hormone replacement therapy (HRT) and risk of invasive ductal and lobular breast carcinoma

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Ever use</th>
<th>6 months–4.9 years</th>
<th>5–14.9 years</th>
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<th>Ever use</th>
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<td>1.5 (1.0–2.3)</td>
<td>1.6 (1.0–2.6)</td>
<td>0.9 (0.6–1.3)</td>
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<td>1.2 (0.9–1.6)</td>
<td>0.9 (0.6–1.3)</td>
<td>1.6 (0.9–2.8)</td>
<td>1.5 (0.3–7.1)</td>
</tr>
<tr>
<td>Dailing et al. (2002)</td>
<td>1.0 (0.8–1.3)</td>
<td>1.0 (0.8–1.4)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.2 (0.9–1.6)</td>
<td>1.0 (0.8–1.3)</td>
<td>1.0 (0.7–1.3)</td>
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</tr>
</tbody>
</table>
observed with other breast malignancies (Evans et al.
2002). ILC is associated with a higher incidence of
asymmetric density (3–25%) or architectural distortion
(10–28%) and is often less radiopaque than normal
fibroglandular tissue (Mendelson et al. 1989, Watson
2001). Microcalcifications have been reported only in
1–28% of cases, and frequently represent unrelated
histological lesions such as IDC, ductal carcinoma
in situ and sclerosing adenosis (Mendelson et al. 1989,
Helvie et al. 1993, Krecke & Gisvold 1993). In a
series of 94 ILCs assessed with Mx, 60% of these
lesions manifested as masses, of which 71% were
described as irregular and spiculated; 21% as archi-
tectural distortions; and the remaining 20% as either
asymmetric densities or calcifications (Evans et al.
2002). More recently Boetes et al. (2004) showed that a
mass was visible on Mx only in 58% of the women,
while an architectural distortion was present in 28%.
A large proportion of ILCs have been found to be
visible in one view only, most often the cranio-caudal
view (Cornford et al. 1995).

Ultrasound
The sensitivity of US for the detection of ILC has been
reported to range between 25 and 88% (Paramagul
et al. 1995, Rissanen et al. 1998). Some authors found
that US significantly improves the detection of ILC in
patients presenting with palpable nodules and no
mammographically identified masses (Butler et al.
1999, Evans & Lyons 2000). Others reported that US
has a limited role in ILC because of the variety of US
appearances and a very low sensitivity and specificity
for the diagnosis of small tumours (Chintana et al.
1995). However, a high detection rate by US,
sensitivity of 87.7%, was also found in a series of 81
mammographically subtle or invisible ILCs, although
most of them were not clinically palpable (Butler et al.
1999). The prediction of breast cancer size by US and
Mx is less accurate in lobular than ductal carcinoma
(Golshan et al. 2004). Moreover, US correlation with
pathology has been shown to become less accurate as
tumour size increases (Tresserra et al. 1999).

Magnetic resonance imaging
Further diagnostic difficulties may derive from the
higher rates of multifocal and/or multicentric tumours
when compared with ductal carcinoma and the
associated higher incidence of synchronous and/or
metachronous controlateral disease, typical of lobular
histology (Cornford et al. 1995, Sastre-Garau et al.
Several studies have demonstrated that MRI detects
additional malignancy occult on Mx and separate from
the primary tumour site or in the controlateral breast in
16–58% of patients with ILC (Rodenko et al. 1996,
Esserman et al. 2002, Kneeshaw et al. 2003, Quan
compared 20 mastectomy specimens of ILC serially
sectioned in a sagittal plane with the preoperative MRI
sagittal images, showing a highly significant corre-
lation between MRI and pathology, with 85%
agreement by size and location of multifocal/multi-
centric lesions, when compared with 27–36% obtained
with Mx alone. It was also noted that MRI was able to
detect unsuspected skin extension not seen by Mx,
whereas it appeared to overestimate the presence of
chest-wall invasion (Rodenko et al. 1996). This high
sensitivity of MRI has been demonstrated to affect
remarkably the management of ILC, often producing
variations in the surgical planning. In a large study on
463 women, Fischer et al. reported a change in
management of 14.3% of the patients with ILCs
following MRI due to the presence of more extensive
disease (Fisher et al. 1999). In a series of 267 patients
with primary breast tumours, patients with lobular
histology were twice as likely to experience a change
in therapy based on improved MRI staging when
compared with patients who had all other histological
subtypes (Bedrosian et al. 2003). The majority of these
patients with ILCs were converted to mastectomy and
MRI suspicion of malignancy was validated patho-
logically in 82% of the cases (Bedrosian et al. 2003).

Fine needle aspiration
The reported false negative rate in fine needle aspiration
(FNA) of ILC ranges from 15% to ~60% with a
sensitivity of 60.5–76%, considerably lower than that of
IDCs (Schelfout et al. 2004). A false negative core
biopsy is also more likely because of the difficult in the
localization of the lesions and the sparse cellularity of
the tumour (Pointon & Cunningham 1999). The lower
sensitivity of FNA in ILC appears to be due to sampling
and interpretative errors, caused by tumour specific
factors such as the characteristic low-grade atypia, the
small-sized cells and the histological type of ILC
(classic versus non-classic; Hwang et al. 2004, Molland
et al. 2004). The cytologic cellularity of the lesion does
not reflect the actual cellularity of the tumour, but
instead is an indicator of the architectural arrangement
of the neoplastic cells. Tumours that form epithelial cell
groups, such as in non-classic ILC, tend to yield more
cellular aspirates that are diagnostic for carcinoma.
In contrast, classic ILC, in which single neoplastic cells
are embedded in fibrous stroma, is more likely to yield
a paucicellular smear with subtle atypia and rare single intact epithelial cells (Hwang et al. 2002).

### Biological and clinical features of invasive lobular cancer

Several data substantiate that ILC has distinctive clinical and biological features when compared with IDC. The incidence of oestrogen and progesterone receptors positivity in ILC varies from 43 to 96% and 42 to 82% respectively which is higher than IDC (Coradini et al. 2002, Cocquyt et al. 2003, Mersin et al. 2003, Arpino et al. 2004, Korhonen et al. 2004, Mathieu et al. 2004, Molland et al. 2004; Table 4). These data are consistent with the growing body of evidence that HRT use is associated with a greater increase in risk of ILC when compared with IDC (Li et al. 2000a,b, 2003a,b,c, Chen et al. 2002, Daling et al. 2002, Newcomb et al. 2002, Newcomer et al. 2003). In fact, it has been reported that the use of HRT is associated with increased risks of estrogen receptor (ER)+/PR+ tumours, while HRT use does not influence the risk of either ER+/PR− or ER−/PR−– tumours, thus suggesting that HRT may promote breast cancer through the stimulation of both ERs and PRs, and not through the ER alone (Li et al. 2003c).

ILC occurs more frequently in older patients and is larger in size than IDC (Sastre-Garau et al. 1996, Mersin et al. 2003, Arpino et al. 2004). The older age at diagnosis of patients with ILC may be due to a low proliferative rate or greater difficulties in detecting ILC. These diagnostic difficulties may also account for the higher incidence of ILCs reported in patients with initially metastatic breast carcinoma (Jimeno et al. 2004). Despite the larger size of ILC, it has been observed that the rate of lymph nodal involvement is the same or even slightly lower when compared with IDC (Mersin et al. 2003, Arpino et al. 2004, Korhonen et al. 2004).

Several studies have shown that ILC is frequently C-ErbB-2 negative, bcl-2 positive and p53 negative (Frolik et al. 2001, Coradini et al. 2002, Cocquyt et al. 2003, Arpino et al. 2004, Korhonen et al. 2004, Mathieu et al. 2004; Table 5). In addition, the proliferative activity and lymphatic-vascular invasion rate are lower in ILC and VEGF is more frequently under-expressed, thus suggesting that ILC has more favourable biological features when compared with IDC (Frolik et al. 2001, Coradini et al. 2002, Mersin et al. 2003, Arpino et al. 2004, Mathieu et al. 2004, Molland et al. 2004; Table 5).

Amplification and/or overexpression of the C-ErbB-2 or HER2/neu oncogene occur in 20–30% of invasive breast tumours and are associated with shortened survival and reduced time to disease recurrence and lower sensitivity to chemotherapy (Abd El-Rehim et al. 2004, Linderholm et al. 2004). Also the proliferation markers, like Ki67 (MIB1), S-phase fraction, thymidine labelling index (TLI) and mitotic activity index (MAI) have been shown to be independent prognostic factors for recurrence-free survival and/or overall survival (OS; Caly et al. 2004, van Diest et al. 2004). The p53 protein plays a pivotal role in the cellular response to DNA-damaging events. P53 overexpression has been correlated with higher histological breast tumour grade and lower overall and disease-free survival in breast cancer patients (Gurkan et al. 2004). Bcl-2 positivity in breast tumours entails a more favourable clinical course with lower frequency of lymph node metastasis and longer survival, whereas this suggestion may not apply to the pleomorphic lobular carcinoma subtype which is a variant of ILC characterized by poor prognosis (Frolik et al. 2001).

The aggressive behaviour and the consequent poor prognosis of pleomorphic lobular carcinoma, reported in many series, have been attributed to the more frequent overexpression of HER2 and the generally

### Table 4 Expression of oestrogen and progesterone receptors in lobular and ductal carcinoma

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No of patients</th>
<th>ER positive</th>
<th>PgR positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ILC</td>
<td>IDC</td>
<td>ILC (%)</td>
</tr>
<tr>
<td>Korhonen et al. (2004)</td>
<td>295</td>
<td>295</td>
<td>244 (92)</td>
</tr>
<tr>
<td>Molland et al. (2004)</td>
<td>182</td>
<td>1612</td>
<td>144 (92)</td>
</tr>
<tr>
<td>Mathieu et al. (2003)</td>
<td>38</td>
<td>419</td>
<td>29 (91)</td>
</tr>
<tr>
<td>Arpino et al. (2004)</td>
<td>4140</td>
<td>45 169</td>
<td>92.7% a</td>
</tr>
<tr>
<td>Cocquyt et al. (2003)</td>
<td>26</td>
<td>101</td>
<td>19 (79)</td>
</tr>
<tr>
<td>Mersin et al. (2003)</td>
<td>65</td>
<td>445</td>
<td>26 (43.3)</td>
</tr>
<tr>
<td>Coradini et al. (2002)</td>
<td>67</td>
<td>190</td>
<td>64 (96)</td>
</tr>
</tbody>
</table>

ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; NS, not significant; NA, information not available.

*These values are expressed by the authors exclusively in percentage.
| Author (year)          | ILC | IDC | ILC (%)  | IDC (%) | P value | ILC (%)  | IDC (%) | P value | ILC (%) | IDC (%) | P value | S-phase fraction | P value |
|------------------------|-----|-----|----------|---------|---------|----------|---------|---------|---------|---------|---------|---------|-----------------|---------|
| Arpino et al. (2004)   | 4140| 169 | 10.7% a  | 24.4%   | <0.0001 | 25.6%    | 53.5%   | <0.0001 | –       | –       | –       | S       | L 68.6%          | <0.0001 |
| Mathieu et al. (2004)  | 19  | 110 | 1 (5)    | 37 (34) | 0.012   | 1 (5)    | 52 (47) | <0.001  | –       | –       | –       | K       | I 19.2%          | 0.01    |
| Korhonen et al. (2004) | 295 | 295 | 9 (4)    | 58 (22) | <0.001  | –        | –       | –       | –       | –       | –       | K       | H 12.2%          | 0.001   |
| Molland et al. (2004)  | 182 | 1612| –        | –       | –       | –        | –       | –       | –       | –       | –       | K       | 14%             | 0.001   |
| Cocquyt et al. (2003)  | 26  | 101 | 1 (4)    | 25 (18) | 0.04    | 3 (17)   | 12 (19) | 0.84    | –       | –       | –       | K       | 17 (89)         | 0.01    |
| Mersin et al. (2003)   | 65  | 445 | –        | –       | –       | –        | –       | –       | –       | –       | –       | K       | 19 (89)         | 0.004   |
| Coradini et al. (2002) | 67  | 190 | –        | –       | –       | –        | –       | –       | 4 (6)   | 46 (24) | <0.005  | TLI     | 19 (28)         | <0.005  |
| Frolik et al. (2001)   | 15  | 15  | 1 (6.6)  | 2 (13)  | NA      | 5 (33)   | 6 (40)  | NA      | 15 (100)| 6 (40)  | NA      | MIB-1   | 2.19%           | 0.0001  |

L, low intermediate and high S-phase fraction; TLI, thymidine labelling index; PLC, pleomorphic lobular carcinoma; NA, information not available; NS, not significant.

*These values are expressed by the authors exclusively in percentage.
low apoptosis rate. Moreover, the pleomorphic appearance of this variant hinders its correct identification and differentiation from ductal carcinoma (Frolik et al. 2001).

**Surgical treatment of invasive lobular cancer**

**Breast conservative surgery and mastectomy**

The clinicopathological features of ILC and the higher rates of multifocal and multicentric lesions when compared with IDC, ranging from 4.5 to 31%, had led to questioning the effectiveness of breast-conservative surgery (BCS; Sastre-Garau et al. 1996, Toikkanen et al. 1997, Hussien et al. 2003). The suggestion for mastectomy as a safer option to control local disease in patients with ILC was based on the higher local recurrence rates after BCS when compared with IDC reported in some old series (Mate et al. 1992). Many other authors were not able to confirm this difference (Kurtz et al. 1989, Schnitt et al. 1989, Poen et al. 1992, Weiss et al. 1992, Silverstein et al. 1994, White et al. 1994, Sastre-Garau et al. 1996, Bouvet et al. 1997, Haffty et al. 1997, Salvadori et al. 1997, Peiro et al. 2000, Molland et al. 2004, Santiago et al. 2005, Vo et al. 2006; Table 6). Several factors have been demonstrated to affect local recurrence after BCS and it is generally recognized that positive margins are one of the most important determinants of local recurrence (Hussien et al. 2003, Chagpar et al. 2004, Horst et al. 2005). The histological subtype has been found to affect margin status in some reports (Mai et al. 2000, Park et al. 2000), but not in others (Horiguchi et al. 1999). A large study on 2658 patients treated with lumpectomy has confirmed that patients with lobular histology are at higher risk for positive margins and, therefore, may require a wider initial resection (Chagpar et al. 2004). The insidious histological growth pattern of ILC with malignant cells infiltrating singly or in small clusters the normal breast makes the gross extent of disease difficult to define at operation (Chagpar et al. 2004, Fleming et al. 2004). Fleming et al. have recently reported a significant difference between the median macroscopic (20 mm) and the median microscopic (25 mm) tumour size in patients with ILC. Moreover, the macroscopic intraoperative margin assessment was less successful in ILC with a sensitivity and specificity of 0.6 and 0.83 respectively when compared with IDC sensitivity of 0.8 and a specificity of 0.93 (Fleming et al. 2004).

Nonetheless, during the past few years, the treatment of ILC has evolved away from mastectomy towards BCS as well as IDC. Breast conservation has also been prompted by the evidence that the type of surgery does not affect short- or long-term survival (Weiss et al. 1992, Holland et al. 1995, Sastre-Garau et al. 1996, Hussien et al. 2003, Molland et al. 2004).

At present, only few studies have compared BCS and mastectomy in patients with ILC (Du Toit et al. 1991, Holland et al. 1995, Warneke et al. 1996, Chung et al. 1997, Hussien et al. 2003, Singletary et al. 2005; Table 7). Most authors have concluded that ILC can be safely treated with BCS with no difference in local recurrence (Holland et al. 1995, Warneke et al. 1996, Chung et al. 1997). Furthermore, the two studies that have found a significant increase of local recurrence rates in patients with ILC after BCS should hardly be taken into account because of the inexplicably high recurrence rates of about 40% (Du Toit et al. 1991, Hussien et al. 2003).

**Management of contralateral breast cancer risk**

The reported incidence rate of contralateral ILC varies from 2.7 to 23% (Du Toit et al. 1991, Sastre-Garau et al. 1996, Arpino et al. 2004). For this reason the management of contralateral breast cancer risk in patients diagnosed with ILC is still controversial and have ranged from prophylactic mastectomy to random contralateral breast biopsy to follow-up with investigation of any suspicious lesion (Lee et al. 1995). Nevertheless, a careful pre- and post-operative assessment of the contralateral breast in patients with ILC is mandatory, especially in the light of more recent data. Polednak has assessed 300 patients with bilateral synchronous breast carcinoma (BSBC) and 13 495 patients with unilateral breast carcinoma recorded between 1995 and 1999 at the Connecticut Tumour Registry. Lobular histology was significantly more frequent in BSBC patients and, although length of follow-up was limited, the risk of death was higher in BSBC (RR: 1.43, P<0.05) than in unilateral patients (Polednak 2003). In a retrospective review of 239 patients with unilateral early stage breast carcinoma who underwent contralateral prophylactic mastectomy, ILC in the index breast was a major determinant of contralateral breast tumours (Goldflam et al. 2004).

**Sentinel lymph node biopsy feasibility and accuracy of intraoperative assessment**

The presence of axillary lymph node metastases is the most significant prognostic factor for patients with early stage breast cancer. The specific nature of ILC, as difficult to detect and often multifocal and/or multicentric, has brought into question the feasibility of nodal staging with sentinel node biopsy (SNB). Moreover,
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No of patients</th>
<th>Stage</th>
<th>5-year LRR (%)</th>
<th>10-year LRR (%)</th>
<th>Median follow-up (months)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vo et al. (2006)</td>
<td>84</td>
<td>I,II</td>
<td>1</td>
<td>7</td>
<td>145</td>
<td>NS</td>
</tr>
<tr>
<td>Santiago et al. (2005)</td>
<td>55</td>
<td>I,II</td>
<td>14</td>
<td>18</td>
<td>108</td>
<td>NS</td>
</tr>
<tr>
<td>Molland et al. (2004)</td>
<td>182</td>
<td>I,II</td>
<td>3.9</td>
<td>15</td>
<td>133</td>
<td>NS</td>
</tr>
<tr>
<td>Peiro et al. (2000)</td>
<td>93</td>
<td>I,II</td>
<td>–</td>
<td>–</td>
<td>137</td>
<td>NS</td>
</tr>
<tr>
<td>Salvadori et al. (1997)</td>
<td>286</td>
<td>I,II</td>
<td>–</td>
<td>8</td>
<td>–</td>
<td>NS</td>
</tr>
<tr>
<td>Haffty et al. (1997)</td>
<td>54</td>
<td>I,II</td>
<td>10</td>
<td>–</td>
<td>126</td>
<td>NS</td>
</tr>
<tr>
<td>Bouvet et al. (1997)</td>
<td>74</td>
<td>NA</td>
<td>12</td>
<td>–</td>
<td>56</td>
<td>NA</td>
</tr>
<tr>
<td>Sastre-Garau et al. (1996)(^a)</td>
<td>480</td>
<td>I,II</td>
<td>–</td>
<td>9</td>
<td>14(^b)</td>
<td>NS</td>
</tr>
<tr>
<td>White et al. (1994)</td>
<td>30</td>
<td>I,II</td>
<td>3.3</td>
<td>–</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Silverstein et al. (1994)</td>
<td>161</td>
<td>I,II</td>
<td>5(^c)</td>
<td>7</td>
<td>78</td>
<td>NS</td>
</tr>
<tr>
<td>Weiss et al. (1992)</td>
<td>41</td>
<td>I,II</td>
<td>9.7</td>
<td>–</td>
<td>61</td>
<td>NS</td>
</tr>
<tr>
<td>Poen et al. (1992)</td>
<td>60</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
<td>66</td>
<td>NA</td>
</tr>
<tr>
<td>Schnitt et al. (1989)</td>
<td>49</td>
<td>I,II</td>
<td>12</td>
<td>–</td>
<td>75</td>
<td>NS</td>
</tr>
<tr>
<td>Kurtz et al. (1989)</td>
<td>67</td>
<td>I,II</td>
<td>13.5</td>
<td>–</td>
<td>71</td>
<td>NS</td>
</tr>
<tr>
<td>Mate et al. (1986)</td>
<td>12</td>
<td>I,II</td>
<td>25</td>
<td>–</td>
<td>82.8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

NS, not significant; NA, information not available.

\(^a\)Most patients in this series were treated with conservative surgery and radiation therapy, but some were treated with conservative surgery alone and some were treated with radiation therapy alone.

\(^b\)This group includes all non-lobular infiltrating carcinomas.

\(^c\)The local recurrence rates (LRR) are at 7 years.
because ILC usually has low mitotic rate with uniform appearance of bland tumour cells that lack cellular atypia, and tends to infiltrate lymph nodes in a single cell pattern, the distinction between lobular carcinoma cells and lymphoid cells can be extremely challenging (Cocquyt & Van Belle 2005). Therefore, particular attention should be given to histological specimens of lobular carcinomas because nodal metastases are more often missed with ILC, and false negative results are more frequently reported when compared with ductal carcinomas (Cocquyt & Van Belle 2005). Old studies have excluded patients with multifocal breast tumour on the assumption that tumours located in different breast quadrants drain to different sentinel lymph nodes and, therefore, SNB would result in inaccurate axillary lymph node staging. Conversely, different techniques adopting subareolar and peritumoural injection sites have demonstrated the identification of the same sentinel node, thus suggesting that the drainage of the different quadrants of the breast have a final common lymphatic pathway to the axilla (Tuttle et al. 2002). A recent analysis of 75 patients with multifocal tumours and 559 patients with unifocal tumours did not show any difference in the false negative rate, overall accuracy and negative predictive value of the SNB technique between the multifocal and the unifocal groups (Goyal et al. 2004).

A prospective study have compared the detection rates and false negative rates in patients with ILC and IDC of SNB; the false negative rate was 7.6% for IDC and 9% for ILC (Classe et al. 2004).

Creager et al. have evaluated the intraoperative imprint cytology of sentinel lymph nodes for ILC. The sensitivity of this technique for ILC was 52%, the specificity 100% and the accuracy 82%. Compared with IDC, these parameters were not significantly different. However, the sensitivity for detecting micrometastasis of ILC was only 25% (Creager & Geisinger 2002). Hence, if micrometastases are used to determine the need for further axillary dissection, more sensitive intraoperative tools will be necessary to avoid a second surgical intervention. Despite these limitations, SNB can be considered a valuable and accurate technique to stage the axilla in ILC.

### Preoperative chemotherapy (PCT) in invasive lobular cancer

PCT is a widely accepted treatment for patients presenting with locally advanced breast cancer in order to downstage the tumour and facilitate breast conserving surgery. Clinical and pathological responses and pathologic nodal status after PCT are considered predictive for survival (Rouzier et al. 2004). Moreover, PCT allows the assessment of tumour response in vivo and consequently provides an opportunity to predict outcome and tailor therapy (Kaufmann et al. 2003).

Clinical and pathological responses to PCT are less frequent in ILC compared with IDC (Cocquyt et al. 2003, Mathieu et al. 2004, Cristofanilli et al. 2005, Tubiana-Hulin et al. 2006; Table 8). In a recent study, the difference in pathological response rates between ILC and IDC persists even after adjusting for hormone receptor status and use of taxanes (Cristofanilli et al. 2005). Cocquyt et al. have assessed responses to primary chemotherapy in 135 patients with breast tumours larger than 3 cm on clinical examination. Overall clinical and pathological response were significantly higher in IDC, when compared with ILC (75 vs 50%, \( P = 0.0151 \)) and the type of PCT did not affect this result. The estimated odds of having a response were approximately three times higher.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No of patients with</th>
<th>5-year local recurrence after mastectomy (%)</th>
<th>5-year local recurrence after breast conservative surgery (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singletary et al. (2005)</td>
<td>21,596a</td>
<td>2.6b</td>
<td>5.4b</td>
<td>NS</td>
</tr>
<tr>
<td>Hussien et al. (2003)</td>
<td>129</td>
<td>5</td>
<td>42.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chung et al. (1997)</td>
<td>316</td>
<td>4.3</td>
<td>2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Warneke et al. (1996)</td>
<td>111</td>
<td>3</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Holland (1995)</td>
<td>226</td>
<td>12</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Du Toit et al. (1991)</td>
<td>171</td>
<td>27.6</td>
<td>42</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

NS, not significant.

a Patients with ILC were selected from the National Cancer Data Base (1989–2001).

b These values are the 5-year local recurrence rates referred to T1/node negative patients who were diagnosed with ILC in the 1989–1990.

c These values are the 5-years local recurrence rates referred to T1/node negative patients who were diagnosed with ILC in the 1994–1995.

### Table 7 Local recurrence after breast conservative surgery and mastectomy in patients with invasive lobular carcinoma (ILC)

<table>
<thead>
<tr>
<th>No of patients with ILC</th>
<th>5-year local recurrence after mastectomy (%)</th>
<th>5-year local recurrence after breast conservative surgery (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singletary et al. (2005)</td>
<td>21,596a</td>
<td>2.6b</td>
<td>5.4b</td>
</tr>
<tr>
<td>Hussien et al. (2003)</td>
<td>129</td>
<td>5</td>
<td>42.8</td>
</tr>
<tr>
<td>Chung et al. (1997)</td>
<td>316</td>
<td>4.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Warneke et al. (1996)</td>
<td>111</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Holland (1995)</td>
<td>226</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Du Toit et al. (1991)</td>
<td>171</td>
<td>27.6</td>
<td>42</td>
</tr>
</tbody>
</table>

NS, not significant.

a Patients with ILC were selected from the National Cancer Data Base (1989–2001).

b These values are the 5-year local recurrence rates referred to T1/node negative patients who were diagnosed with ILC in the 1989–1990.

c These values are the 5-years local recurrence rates referred to T1/node negative patients who were diagnosed with ILC in the 1994–1995.
Table 8 Clinical and pathological response of invasive lobular carcinoma (ILC) to preoperative chemotherapy compared with invasive ductal carcinoma (IDC)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ILC n=118 (%)</td>
<td>IDC n=742 (%)</td>
<td>ILC n=122 (%)</td>
<td>IDC n=912 (%)</td>
</tr>
<tr>
<td>Clinical response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>–</td>
<td>–</td>
<td>4 (3)</td>
<td>142 (16)</td>
</tr>
<tr>
<td>Partial</td>
<td>–</td>
<td></td>
<td>10 (26.3)</td>
<td>206 (49.2)</td>
</tr>
<tr>
<td>Stable</td>
<td>–</td>
<td>118 (97)</td>
<td>28 (73.7)</td>
<td>10 (38)</td>
</tr>
<tr>
<td>Progression</td>
<td>–</td>
<td>769 (84)</td>
<td>28 (6.7)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Other</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>P value</td>
<td>–</td>
<td>–</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Pathological response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>2 (1)</td>
<td>67 (9)</td>
<td>4 (3)</td>
<td>138 (15)</td>
</tr>
<tr>
<td>Other</td>
<td>116 (99)</td>
<td>675 (91)</td>
<td>118 (97)</td>
<td>770 (85)</td>
</tr>
<tr>
<td>P value</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.0066</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative surgery</td>
<td>35 (30)</td>
<td>456 (48)</td>
<td>20 (16)</td>
<td>263 (29)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>83 (70)</td>
<td>386 (52)</td>
<td>101 (83)</td>
<td>614 (67)</td>
</tr>
<tr>
<td>P value</td>
<td>0.006</td>
<td>0.003</td>
<td>0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant.
for patients with IDC than for patients with ILC (Cocquyt et al. 2003). Consistent with these findings, Mathieu et al. (2004) reported that clinical response to PCT was lower for ILC when compared with IDC (26 vs 58%, P = 0.001) and none of the 38 patients diagnosed with ILC had a complete pathological response after PCT (Table 8).

The profile of biological markers expression in ILC may be considered the turning point to understand the lower response rates and the poor chemosensitivity to PCT of ILC (Cocquyt et al. 2003, Mathieu et al. 2004, Cristofanilli et al. 2005). In one study ER expression, higher histological grade, p53 overexpression and high Ki67 rate were significantly associated with the clinical response and the pathological response to PCT (Mathieu et al. 2004). The proliferative activity was the most significant factor associated with both clinical and pathological response, as high proliferative rates were found to predispose to a higher response to chemotherapy (Mathieu et al. 2004). Interestingly, the lack of chemosensitivity of ILC does not result in worse survival rates when compared with IDC (Cristofanilli et al. 2005). However, the lower response rates to PCT of ILC determine larger tumour residual volumes, thereby producing a greater risk of local recurrence. Cocquyt et al. (2003) reported in a group of tumours with similar diameters before chemotherapy, higher pathologic diameters at the end of chemotherapy for ILC when compared with IDC (3.95 vs 2.73 cm). Furthermore, ILC is more likely to require rescue mastectomy after PCT when compared with IDC because of positive margins, thus showing that the differences in the choice of primary surgery between ILC and IDC are not erased by PCT (Cocquyt et al. 2003, Mathieu et al. 2004, Cristofanilli et al. 2005, Tubiana-Hulin et al. 2006). These data are crucial because the high rates of breast conservative surgery are the only demonstrated benefit resulting from neoadjuvant chemotherapy (Cristofanilli et al. 2005). Moreover, poor response to PCT is not linked to worse survival, so chemotherapy response does not seem to have an impact on survival in ILC in the same way as it does for patients with IDC (Cristofanilli et al. 2005, Tubiana-Hulin et al. 2006).

### Prognosis of patients with invasive lobular cancer

#### Comparative disease-free and OS in ILC and IDC

The 5-year OS and disease-free survival (DFS) rates for patients with ILC ranges from 68 to 87% and 73 to 98% respectively (Silverstein et al. 1994, Sastre-Garau et al. 1996). This variability might be due to the

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No. of patients</th>
<th>5-year DFS</th>
<th>5-year OS</th>
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<tbody>
<tr>
<td></td>
<td>ILC</td>
<td>IDC</td>
<td>ILC (%)</td>
</tr>
<tr>
<td>Santiago et al. (2005)</td>
<td>55</td>
<td>1093</td>
<td>98</td>
</tr>
<tr>
<td>Arpino et al. (2004)</td>
<td>4140</td>
<td>45 169</td>
<td>85.7</td>
</tr>
<tr>
<td>Korhonen et al. (2004)</td>
<td>295</td>
<td>295</td>
<td>75</td>
</tr>
<tr>
<td>Molland et al. (2004)</td>
<td>182</td>
<td>1612</td>
<td>87.9</td>
</tr>
<tr>
<td>Ugnat et al. (2004)</td>
<td>233</td>
<td>1765</td>
<td>NA</td>
</tr>
<tr>
<td>Mersin et al. (2003)</td>
<td>65</td>
<td>445</td>
<td>71</td>
</tr>
<tr>
<td>Winchester et al. (1998)</td>
<td>10 676</td>
<td>145 220</td>
<td>98</td>
</tr>
<tr>
<td>Toikkanen et al. (1997)</td>
<td>217</td>
<td>1121</td>
<td>NA</td>
</tr>
<tr>
<td>Silverstein et al. (1994)</td>
<td>161</td>
<td>1138</td>
<td>74</td>
</tr>
</tbody>
</table>

NS, not significant; NA, information not available.
discrepancy in the histological criteria used to define ILC, to the relatively small numbers of patients and to differences in the adjuvant therapies used across the studies (Cristofanilli et al. 2005).

Intuitively, the more favourable prognostic factors of ILC would translate into a survival advantage for patients with ILC. Nonetheless, many studies have shown that the survival rates are not significantly different in ILC and IDC and only in few old studies ILC has statistically significant better OS and DFS than IDC (Silverstein et al. 1994, Toikkanen et al. 1997, Winchester et al. 1998, Mersin et al. 2003, Arpino et al. 2004, Korhonen et al. 2004, Molland et al. 2004, Ugnat et al. 2004, Santiago et al. 2005; Table 9).

Whether histological type is a prognostic factor in the breast carcinoma and a major parameter in the therapeutic decision-making process is still controversial also in more recent studies.

In a retrospective cohort study on 164 958 women diagnosed with breast cancer in the SEER cancer registries from 1974 to 1998, lobular tumours were associated with a risk of mortality 11% lower than IDC. The magnitude of this lower risk increased over time, as ILC was associated with an 8% lower risk of mortality when compared with IDC between 1974 and 1983, and a 24% lower risk between 1994 and 1998 (Li et al. 2003d). The authors recognized that a limitation of this study was the lack of data concerning the adjuvant hormonal therapy. In fact, lobular tumours are more likely than ductal tumours to be hormone receptor-positive and, therefore, are suitable candidates for hormonal treatment with tamoxifen, which is known to reduce mortality. Hence, the risk of mortality associated with ILC may have decreased as tamoxifen use is increased over the study period (Li et al. 2003d). Similarly, the considerable survival after recurrence reported in some series has been explained by a better response to hormonal treatments of patients with ILC (Arpino et al. 2004, Korhonen et al. 2004). This favourable prognostic impact of ILC has also been confirmed by the 5-year survival analysis conducted on a sample of 4478 breast cancer patients; the RR of death was 0.58 (95% CI 0.37–0.91) for lobular tumours as compared with IDC (Allemani et al. 2004). Conversely, histology failed to achieve significant independent prognostic information in other series (Ugnat et al. 2004, Tubiana-Hulin et al. 2006). Nonetheless, in the 5-year survival analysis of 2192 patients with primary breast cancer registered by the ORCC (OR Cancer Centre), patients diagnosed with ILC had an insignificant better survival trend than patients with IDC (91.02 vs 84.32%). These differences have been explained by more frequent grade 1 lesions in patients with ILC than in those with IDC (Ugnat et al. 2004).

Differences in metastatic behaviour between ILC and IDC

Some authors did not report any difference in metastatic pattern between ILC and IDC (Du Toit et al. 1991), while others have reported significant differences in the rate of visceral recurrences (Borst & Ingold 1993, Sastre-Garau et al. 1996, Mersin et al. 2003).

In the study by Arpino et al. ILC is more likely to metastasize to the peritoneum, ovaries (2.2 vs 0.7%, P = 0.0003) and gastrointestinal tract (4.5 vs 1.1%, P = 0.009). Conversely, the distant nodes, lungs/pleura and central nervous system are more frequently involved in IDC (Arpino et al. 2004). Korhonen et al. (2004) have confirmed this tendency of ILC to metastasize to the genital organs and gastrointestinal tract (16% for ILC versus 1% for IDC, P = 0.002), whereas no difference was observed in liver, bone or pulmonary-pleural recurrences. In these two studies the authors reported only few metastases to the endocrine organs, whereas an autopsy study found endocrine metastases in 91% patients with metastatic ILC and in 58% patients with IDC (Bumpers et al. 1993). This is probably due to the fact that most endocrine metastases are silent during lifetime and will not be diagnosed (Korhonen et al. 2004).

The median interval between diagnosis and presentation of metastases from breast carcinoma to the gastrointestinal tract varies in most series from 5 to 6 years, although 10 years or more have rarely been reported (Bamias et al. 2001). The clinical presentation of metastatic disease to the gastrointestinal tract is not definite. Symptoms may be non-specific or striking similar to that of primary gastrointestinal malignancies such as obstruction, haemorrhage or perforation (Lagendijk et al. 1999). For this reason, endoscopy should be performed in all cases of suspected colorectal metastatic lesions in order to accurately detect their site and because endoscopic appearance of metastatic lesions may differ from that of a primary carcinoma. In a review, the metastases to the gastrointestinal tract have been found to appear as diffuse thickening and rigidity of the colonic wall mimicking plastic limitis, Crohn’s-like appearance and ulcerated or nodular areas rather than solitary, discrete masses (Bamias et al. 2001). Histologically, metastases from lobular tumours often do not form glands or tubular structures but infiltrate as small nests and strands of tumour cells, which are usually of the ‘signet-ring’ type. Histopathological diagnosis can be difficult, particularly, for pathologists who are
unaware of the patient’s history and the ‘signet-ring’ morphology of lobular carcinoma may be confused with other primary tumours such as gastric carcinoma. Nonetheless, metastatic ILCs are usually positive for gross cystic disease fluid protein-15, ER and PgR, in contrast with most colorectal or gastric carcinomas, which are negative (Lagendijk et al. 1999, Bamias et al. 2001). The reported differences in metastatic pattern between ILC and IDC could be due to a cell size or shape with physical properties that favour certain areas with microanatomy that is more conducive to stopping or trapping these types of cells. Alternatively, the microenvironment of the ovary or peritoneum may provide growth and survival factors that favour ILC cells over IDC cells (Arpino et al. 2004). Additional molecular or biological differences might account for this peculiar pattern of metastasis. The complete loss of E-cadherin expression has been observed in ILC, in contrast with IDC, in which E-cadherin expression is usually maintained. The loss of E-cadherin expression may result in dehiscence of tumour cells, which would allow easier migration of individual tumour cells into the vasculature. In contrast, persistence of E-cadherin in cells that invade the vasculature could lead to the development of intravascular nests of tumour cells or intravascular emboli. It has been proposed that the former mechanism may be operative in E-cadherin negative IDC and in ILC, whereas the latter may occur in E-cadherin positive IDC (Gupta et al. 2003).

Conclusions

The increased risk for the development of ILC associated with HRT use, if confirmed, might have a rising clinical importance with regard to the diagnosis and the treatment of breast cancer.

ILCs have a substantially increased propensity for multifocal and multicentric distribution and for bilaterality (Sastre-Garau et al. 1996, Toikkanen et al. 1997, Goldflam et al. 2004). Moreover, because of their distinctive growth pattern and biology, lobular carcinomas often fail to form distinct masses that can be easily diagnosed by clinical breast examination or Mx (Rosen 2001). These features can make early diagnosis challenging and breast conservative therapy more difficult.

ILC is generally believed to have more favourable biological features than IDC, with oestrogen and progesterone positive receptors, low grade and low likelihood of lymphatic-vascular invasion. In addition, ILC is characterized by low proliferative activity, C-ErbB-2 negativity, bcl-2 positivity, p53 and VEGF negativity. The lower stage and grade at diagnosis reported in HRT users, who have developed breast cancer when compared with that in non-users, may depend on the higher rate of ILC among HRT users. The lower stage at diagnosis probably reflects also a higher awareness of HRT users for frequent clinical and mammographic screening. Furthermore, women who use HRT tend to belong to the higher socioeconomic classes and have easier access to health facilities (Pappo et al. 2004). Despite the less aggressive biological features of ILC, several studies have not found significant differences in disease-free and OS when compared with IDC (Winchester et al. 1998, Mersin et al. 2003, Arpino et al. 2004, Korhonen et al. 2004, Molland et al. 2004, Santiago et al. 2005).

The role of PCT in ILC should be reconsidered. Only few patients with ILC achieve a pathologic response to PCT and, therefore, may be treated with conservative surgery (Cocquyt et al. 2003, Mathieu et al. 2004, Cristofanilli et al. 2005).

In the following years microarray analysis technology will become undoubtedly an essential tool to understand the role of different patterns of biological markers expression in lobular and ductal breast cancers and to investigate the mechanisms underlying the effect of exogenous steroids on the growth and proliferation of breast cancer.

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