bilateral disease and how it can be used as a unique model to study breast cancer etiology and prognosis.

Methods: By reviewing etiological and outcome studies (n = 35) on bilateral cancer, we identify clinically unique features, fields of research interest and opportunities aimed at improving our understanding of breast cancer etiology, as well as prognosis of the bilateral breast cancer.

Results: Bilateral breast cancer(BBC) occurs in 2−11% of breast cancer patients. Multiple studies evaluating aetiological factors have identified a positive family history, lobular carcinoma, oestrogen receptor negativity, human epidermal growth factor receptor 2 (HER2) positivity and obesity (Body Mass Index of >25 kg/cm^2) as risk factors for metachronous BBC. Age has a contrasting effect on BBC, with increased synchronous tumours but decreased metachronous tumours with increasing age.

There is a strong hormone receptor concordance in BBC, with it being most pronounced in those with synchronous tumours. The identification of microsatellite instability in metachronous BBC suggests a possible relation to the adjuvant treatment of the initial primary breast cancer. Patients treated with adjuvant endocrine therapy after the first primary breast cancer appeared to have a protective effect against metachronous BBC, whilst those who received chemotherapy after the first breast cancer had a worse prognosis after the subsequent breast cancer.

Studies have shown a worse prognosis in those with BBC, particularly in those with synchronous tumours and a shorter time interval (<3 years) between the first and second primary breast cancers. However, the overall survival of metachronous BBC approximates that of unilateral breast cancers when the second primary breast cancer is diagnosed 10 or more years after the first breast cancer.

Conclusion: An ever increasing number of women are at risk of a bilateral cancer, a disease with high risk and relatively poor prognosis, yet our understanding of bilateral disease remains limited with virtually no data from clinical trials. Bilateral cancer offers a biological model to enhance our understanding of breast cancer etiology and outcome.

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Ki67 Proliferation Index in Invasive Lobular Carcinoma of the Breast − Clinicopathologic Correlation and Prognostic Significance

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Background: Invasive lobular carcinoma (ILC) of the breast has distinct clinical and biological characteristics, including lower Ki67, when compared with invasive ductal carcinoma (IDC). Ki67 is an established independent negative prognosticator for disease-free survival and overall survival in IDC, although its role in ILC remains undefined due to lack of dedicated studies.

Material and Methods: We analyzed a consecutive cohort of ILC patients undergoing upfront surgery in a tertiary referral center in Hong Kong between August 2001 and August 2011; patients with pathology other than ILC, metastatic disease or neoadjuvant treatment were excluded. Tumor Ki67 levels were correlated with various clinicopathological parameters and recurrence outcomes. Univariate and multivariate regression analyses were also performed.

Results: A total of 144 patients were included in the analysis. All were female; median age was 50 (range 34−82). Higher Ki67 was significantly associated with higher tumor grade (Spearman correlation coefficient r = 0.2, p = 0.028), tumor size (r = 0.181, p = 0.047), lymphovascular infiltration (r = 0.218, p = 0.031) and lymph node involvement (r = 0.242, p = 0.005). However, there was no significant correlation between Ki67 level and ER, PR or HER2 status. Moreover, Ki67 failed to emerge as an independent predictor of recurrence on univariate and multivariate regression analyses.

Conclusion: In ILC, although high Ki67 correlated with poor-risk pathological features, it did not independently affect recurrence.

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Different Immunohistochemistry-based Subtypes of Early Invasive Breast Cancers in a Monoinstitutional Series: Correlation with Other Known Prognostic Factors, Different Clinical Behavior and Prognosis

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Background: Invasive breast cancer (IBC) is an heterogeneous disease. Gene expression profiling of invasive breast cancer (IBC) has identified several biologically distinct subtypes of IBCs. As proposed by Cheang et al, immunohistochemical (IHC) markers can be used as a surrogate for the molecular classification of breast cancers. Subtypes defined by IHC panel are similar to but not fully identical to intrinsic subtypes and represent a convenient approximation.

Purpose: The aim of our study was to evaluate different clinical behavior, relationship with other clinical-pathological features and survival outcomes for patients (pts) with different subtypes of IBC as classified using four ICH markers (ER, PR, HER2 and Ki67).

Methods: We evaluated data from 3403 cases of IBC treated from 1995 to 2008 classified as: luminal A (positive ER and PR, negative HER2 and Ki67 <14%), luminal B (positive ER and/or PR, negative HER2 and Ki67⩾14%), luminal C (positive ER and/or PR, positive HER2, any Ki67), HER2+ (negative ER and PR, positive HER2, any ki67), triple negative-TN (negative ER and PR, negative HER2, any ki67). Log-rank test and Cox regression model were performed to evaluate the impact of ICH subtypes on overall survival (OS), Event Free Survival (EFS) and their correlation with other known prognostic factors.

Results: We identified 917 (26.9%) luminal A, 1731 (50.9%) luminal B, 279 luminal C (8.2%), 183 (5.4%) HER2+ and 293 (8.6%) triple negative. Median age was 61 years. Luminal A was more frequently (p < 0.001) associated with older age, smaller size, negative axilla involvement, low grading. Observed events (relapses, contralateral and second tumors) were: 54 (6%) in luminal A, 215 (16%) in luminal B, 40 (14%) in luminal C, 42 (23%) in HER2+ and 59 (20%) in triple negative. Disease free interval (DFI) was shorter in luminal C, HER2 and TN (median DFI: 30, 26 and 19 months) than in Luminal A and B (median DFI: 51 and 41 month). Luminal A and B presented more bony and less visceral recurrences than luminal C, HER2 and triple negative tumors. At median follow up of 51 months EFS and OS (p < 0.001) were 94.1 and 95.3% in luminal A, 87.5 and 89% in luminal B, 85.5 and 89.2% in luminal C, 76.8 and 80.9% in HER2+, 79.7% and 81.9% in triple negative. Different subtypes EFS according to nodal status, grading, tumor size and age, were reported in table 1.

Table 1. Subtypes EFS by N, G, size and age

	Luminal A (%)	Luminal B (%)	Luminal C (%)	HER2+ (%)	Triple negative (%)	p
N0	95.5	91.5	92.8	86.2	88.7	0.007
N+	91.3	81.8	75.2	66.3	66.1	<0.001
G1	96.2	89.6	83.3	100.0	81.8	0.09
G2	92.6	89.5	87.4	81.5	83.7	0.195
G3	92.2	83.1	86.3	74.8	79.1	0.02
T1	95.6	91.5	90.7	81.6	86.8	<0.001
T2	88.9	83.4	79.3	72.5	75.9	0.013
T3−4	91.3	73.2	76.5	72.7	55.2	0.015
Age <40	90.5	75.9	75.9	57.9	83.3	0.013
Age 40−55	93.8	88.4	83.5	79.6	76.3	<0.001
Age >55	94.3	87.8	88.8	78.8	81.3	<0.001

Considering only luminal subtypes, Luminal B and C vs Luminal A IBCs were significantly associated with poor EFS in both N0 (p = 0.046) and N+ (p < 0.001), in T1 (p = 0.013) and T2 (p = 0.03), in patients older 40 years (p = 0.002).

Conclusions: IHC-based classification of IBC subtypes is useful for clinical management and it is superior to the WHO classification to define different prognostic groups.