10.2478/v10163-012-0012-x

PROBLEM-SOLVING ARTICLE

Pathology of Breast Cancer: from Classic Concepts to Molecular Pathology and Pathogenesis

Ilze Strumfa*/, Andrejs Vanags***, Arnis Abolins*/**, Janis Gardovskis**/*****
*Department of Pathology, Riga Stradins University, Riga, Latvia
**Institute of Oncology, Riga Stradins University, Riga, Latvia
***Department of Surgery, Riga Stradins University, Riga, Latvia

Summary
Breast cancer has high incidence and still significant mortality. Due to the widespread application and efficacy of surgery in breast cancer treatment, the surgeon has a crucial role in the treatment planning. Taking into account the tendency to personalized cancer care and the heterogeneity of breast cancer, the surgeon has to be aware about the prognostic and predictive characteristics of breast cancer. We discuss here the classaic pathology of breast cancer along with molecular subtypes, novel prognostic markers and molecular pathogenesis.
Key words: breast cancer, pathology, molecular pathology, molecular subtypes, immunohistochemistry

INTRODUCTION

Tissue examination is the gold standard in the tumour diagnostics. Depending on the submitted tissue material, pathology can reveal the presence and spread of the tumour as well as characterise the biological potential as benign or malignant. Up-to-dated techniques and integrated approach to tissue evaluation along with other scientific methods can bring higher volumes of information with high clinical relevance. The morphologic data can predict the potential effect of different treatment modalities. The pathogenesis of tumour also is partially reflected in the neoplastic tissues. a

Breast cancer represents one of the best studied malignant tumours. Considering breast cancer, awareness of pathology is practically important in surgeon's work for planning the treatment. Breast cancer research provides also bright evidence of the possibilities of tissue and integrated investigations in oncology. The level of knowledge in this field could facilitate the development of medical science regarding other malignancies.

The aim of the article is to highlight the classic and modern concepts of breast cancer pathology having clinical implications and / or prognostic value.

DISCUSSION

Breast cancer in surgical practice

Breast cancer is one of the most common malignant tumours in the European population and the most frequent malignancy in female (Bombonati and Sgroi, 2011). Surgery has an important role in the treatment of the primary tumour. In selected cases, patients with metastatic disease also can benefit from surgical treatment (Guarneri and Conte, 2009). However, as the treatment of breast cancer is complex, including surgery as a crucial but not the only step, wider understanding of breast cancer biology is necessary.

Classic pathology of breast cancer

The classics of breast cancer characteristics are represented in the classification of breast tumours by the World Health Organization (Malhotra *et al*., 2010). Traditionally, breast cancer is characterised as *in situ* or invasive regarding the integrity of basement membrane in the former case or loss of it in the second case. This concept is major prognostic value (Bombonati and Sgroi, 2011). At present, cancer *in situ* is described as ductal or lobular. The invasive cancers (listed in Table 1) are classified into ductal, lobular, medullary and other, less frequent types (Figure 1). This classic classification retains prognostic importance and must be invariably applied when evaluating malignant breast tissue.

Besides that, several specific morphological breast cancer types can be associated with specific problems in diagnostics and treatment. Lack of cell cohesion in case of lobular cancer can lead to widespread, still clinically and radiologically silent spread of tumour (Figure 2). Both medullary and mucinous cancer can negatively interfere with diagnostics due to softer consistency by palpation as well as clinical and radiological circumscription in case of medullary cancer, and lower sensitivity of fine needle aspiration (FNA). FNA diagnostics is embarrassed by significant inflammatory infiltrate in medullary cancer as well as by low cellularity and usually low grade in mucinous cancer.

Table 1. Histologic types of invasive breast cancer: characteristics and clinical significance

Histologic type	Frequency, %	Characteristic features	Clinical importance
Ductal cancer	40 – 75	Tubule formation, cellular atypia and mitotic activity are grade-dependant Necrosis can be present Amount of stroma is variable	The most frequent type of breast cancer
Lobular cancer	3.2 – 14 Greatly depends of the applied pathologic criteria	Lack of cellular cohesion • Frequent truncation mutations in *E-Cadherin* gene • Lack of E-Cadherin protein expression by immunohistochemistry • Individual growth of tumour cells or arrangement in files	"Skip lesions" result in higher risk of positive resection margins or unidentified incomplete resection; false impression of multifocality
		Occasional lack of stroma	Difficulties in mammographic detection and / or palpation
		Smaller cells Low mitotic activity Rare necrosis Frequent intracellular mucin More frequently ER+, PR+ Rarely HER2-positive or p53+	More beneficial prognosis if compared with stage-matched ductal carcinomas
Tubular carcinoma	2 – 5	High differentiation: • Tubular architecture (at least 90%) • Lack of myoepithelial cells • Little pleomorphism • Low mitotic rate • More frequently ER+, PR+. Rarely HER2-positive or p53+	Favourable prognosis using strict criteria Difficult morphologic differential diagnosis regarding radial scar and sclerosing or microglandular adenosis
Cribriform carcinoma	2 – 4	• Cribriform architecture • Lack of myoepithelial cells High differentiation: • Little pleomorphism • Low mitotic rate • More frequently ER+, PR+. Rarely HER2-positive or p53+	Favourable prognosis if adhering to strict criteria
Mucinous carcinoma	2 – 3.6	• Neoplastic cells surrounded by pools of extracellular mucus (100%) • Lack of myoepithelial cells High differentiation: • Little pleomorphism • Low mitotic rate • Usually ER+, PR+, HER2-negative and p53-negative	Favourable or excellent prognosis if adhering to strict criteria
Medullary carcinoma	1 – 5	Syncytial growth (at least 75%) Demarcated outline despite true invasive growth Marked stromal infiltration of lymphocytes and plasmocytes Frequent necrosis Mostly ER-, PR-, HER2-negative: triple-negative molecular type p53-positive	Better prognosis if adhering to strict criteria Association with *BRCA1* mutation: histology can be key for genetic evaluation

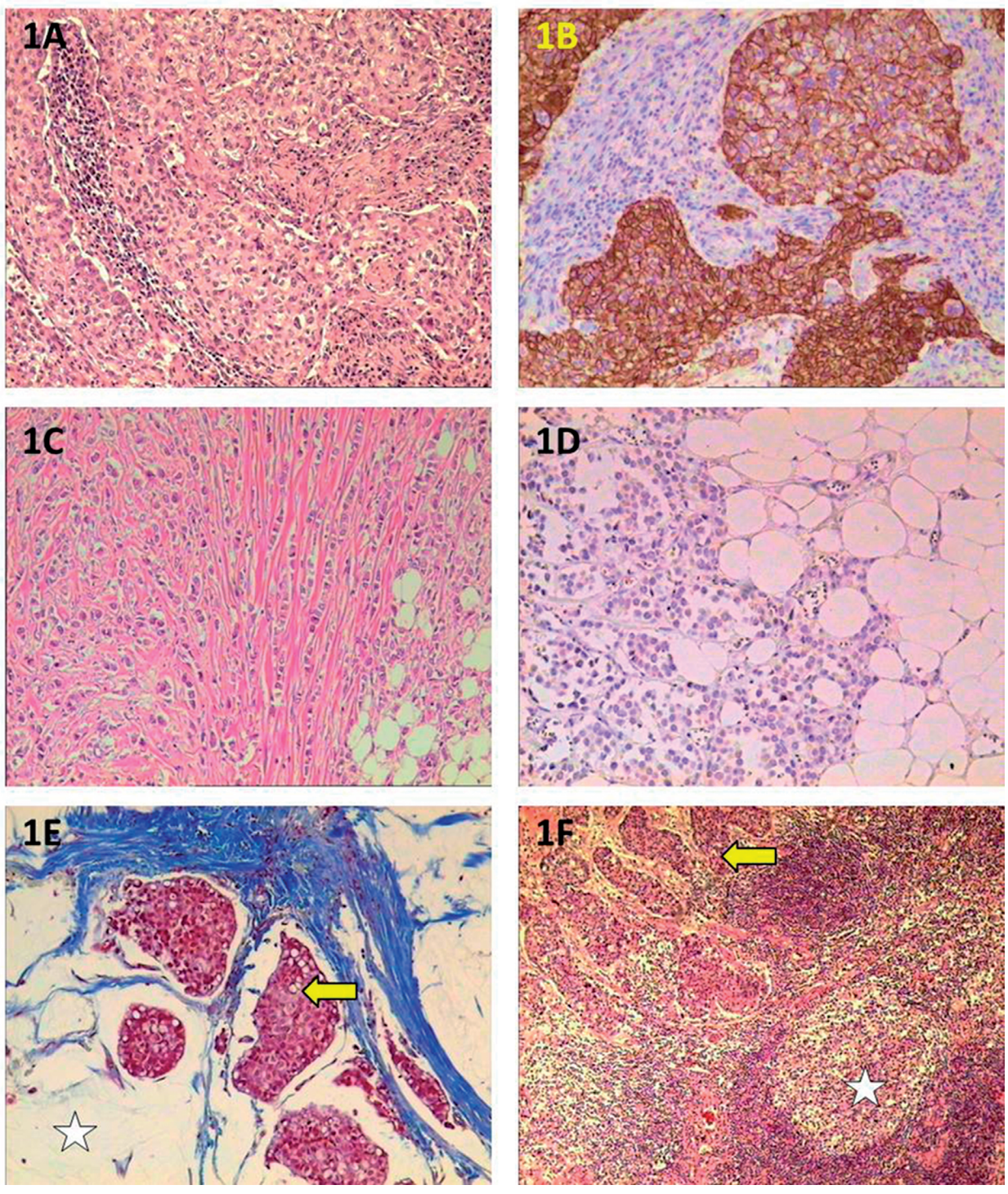

Fig.1. Histological types of breast cancer. A, High-grade ductal cancer. Haematoxylin-eosin (HE), original magnification (OM) 100x. B, Membranous expression of E-Cadherin in ductal cancer confirming the histogenesis even in high-grade case. Immunoperoxidase (IP), anti-E-Cadherin, OM 100x. C, Lobular cancer. HE, OM 100x. D, Lack of E-Cadherin in lobular cancer. IP, anti-E-Cadherin, OM 100x. E. Mucinous cancer. Note the abundance of mucus (star) and lower amount of neoplastic cells (arrow). Masson's trichrome, OM 100x. F, Medullary cancer. Note the presence of lymphoid follicle (star) as well as neoplastic growth (arrow). HE, OM 50x.

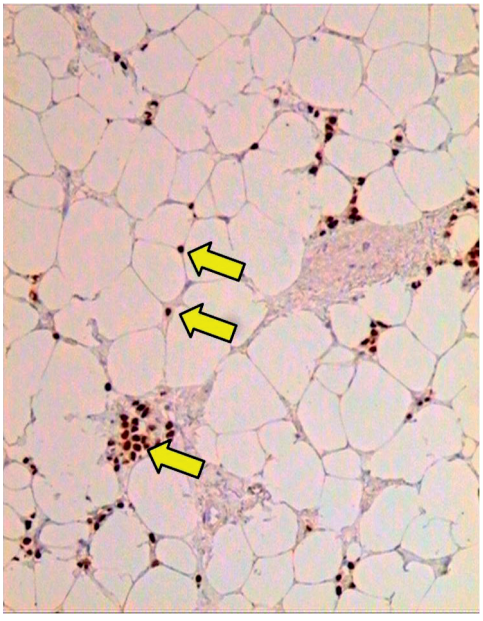

Fig. 2. Marked invasive growth of lobular breast cancer. The tumour cells are highlighted by arrows. IP, anti-estrogen receptor alpha, OM 100x.

Molecular pathology of breast cancer

Breast cancer is a heterogeneous disease including several entities with different clinical behaviour. Even tumours belonging to the same histologic type can have different clinical course. Naturally, the largest group – ductal cancer – shows the highest heterogeneity. Additional information can be obtained from molecular subtyping of breast cancer. This approach is based on expression patterns of so called intrinsic genes (Perou *et al.*, 2000) and results in breast cancer classification into subgroups with different biological properties and response to treatment. The intrinsic genes were defined as genes with higher variation of expression between tumours than within one tumour (Strehl *et al.*, 2011). The genes in breast cancer became up-regulated or down-regulated in larger groups, as will be described further for each molecular subtype. At present, molecular subtyping of breast cancer has become routine practice. The molecular subtypes initially were discovered by gene expression profiling in high throughput microarray technologies (Perou *et al.*, 2000). At present, immunohistochemistry (IHC) is accepted as adequate surrogate marker (Nielsen *et al.*, 2004; Carey *et al.*, 2006) benefitting from higher economic effect and simpler technology despite less robust data in predictive sense (Sorlie, 2004)

The best-known molecular subtypes of breast cancer include luminal or hormone-sensitive, HER2-positive and triple negative tumours (Guarneri and Conte, 2009). The division of luminal subtype into luminal A and luminal B is also well-accepted. The basal or basal-like breast cancer is a matter of active discussions as it overlaps with triple-negative subtype but is not synonymous with it. The other described molecular subtypes include normal-breast like and molecular apocrine subtype.

The luminal molecular subtype (Figure 3) is characterised by estrogen (ER) and progesterone (PR) receptor positivity (Strehl *et al.*, 2011). Luminal subtype can be classified into luminal A and B subtype. The prognostically worse luminal B subtype can be recognised by co-expression of HER2 in addition to ER and PR in contrast to HER2-negative luminal A subtype, or by higher proliferative activity (Cheang *et al.*, 2009; Nielsen *et al.*, 2010; Strehl *et al.*, 2011). In our opinion, diagnostics of luminal B subtype by higher proliferative fraction (reaching or exceeding 14%, as described by Goldhirsch *et al.*, 2011), is less subjective and thus more reliable.

HER2 positive breast cancer (Figure 3) lacks expression of ER and PR, but is defined by HER2 protein over-expression by immunohistochemistry and/or *HER2/neu* gene amplification by *in situ* hybridisation (Strehl *et al.*, 2011). Breast cancer negative for ER, PR and HER2 protein expression is called triple negative (Figure 3). It partially overlaps with basal-like subtype showing expression of basal cytokeratins that normally are present in the basal cell of mammary ducts. High proliferative activity is typical.

New molecular subtypes have also been described. The claudin-low subtype includes triple negative breast cancers lacking also ytokeratin 5/6 and epidermal growth factor receptor in contrast to basal triple negative subtype (Prat *et al.*, 2010; Strehl *et al.*, 2011). The molecular apocrine breast cancers are characterised by ER negativity and androgen receptor positivity in addition to apocrine morphology with presence of intracellular vacuoles (Farmer *et al.*, 2005). In contrast, the initially described normal-breast like subtype is suggested to be the result of specimen contamination by normal tissues (Parker *et al.*, 2009; Weigelt *et al.*, 2010; Strehl *et al.*, 2011).

Each molecular subtype has different biological properties and clinical course. Luminal breast cancer has generally better prognosis (Sorlie *et al.*, 2001; Strehl *et al.*, 2011). It responds to hormonal treatment but show lower chemosensitivity (Rouzier *et al.*, 2005; Peppercorn *et al.*, 2008; Parker *et al.*, 2009; Strehl *et al.*, 2011). Luminal cancer has tendency to relapse in bone or soft tissues. Both HER2-positive and triple negative breast cancer has higher tendency to early development of metastases in visceral location or central nervous system (Guarneri and Conte, 2009). The molecular type also serves as guide for treatment: luminal type can be targeted by hormone therapy, HER2-positive tumours – by anti-HER2 agents, and triple negative – by chemotherapy. Triple-negative breast cancer cells also are dependant of poly (ADP) ribose polymerase (PARP) to repair single strand breaks in DNA, therefore PARP inhibition can be effective treatment modality (Guarneri and Conte, 2009).

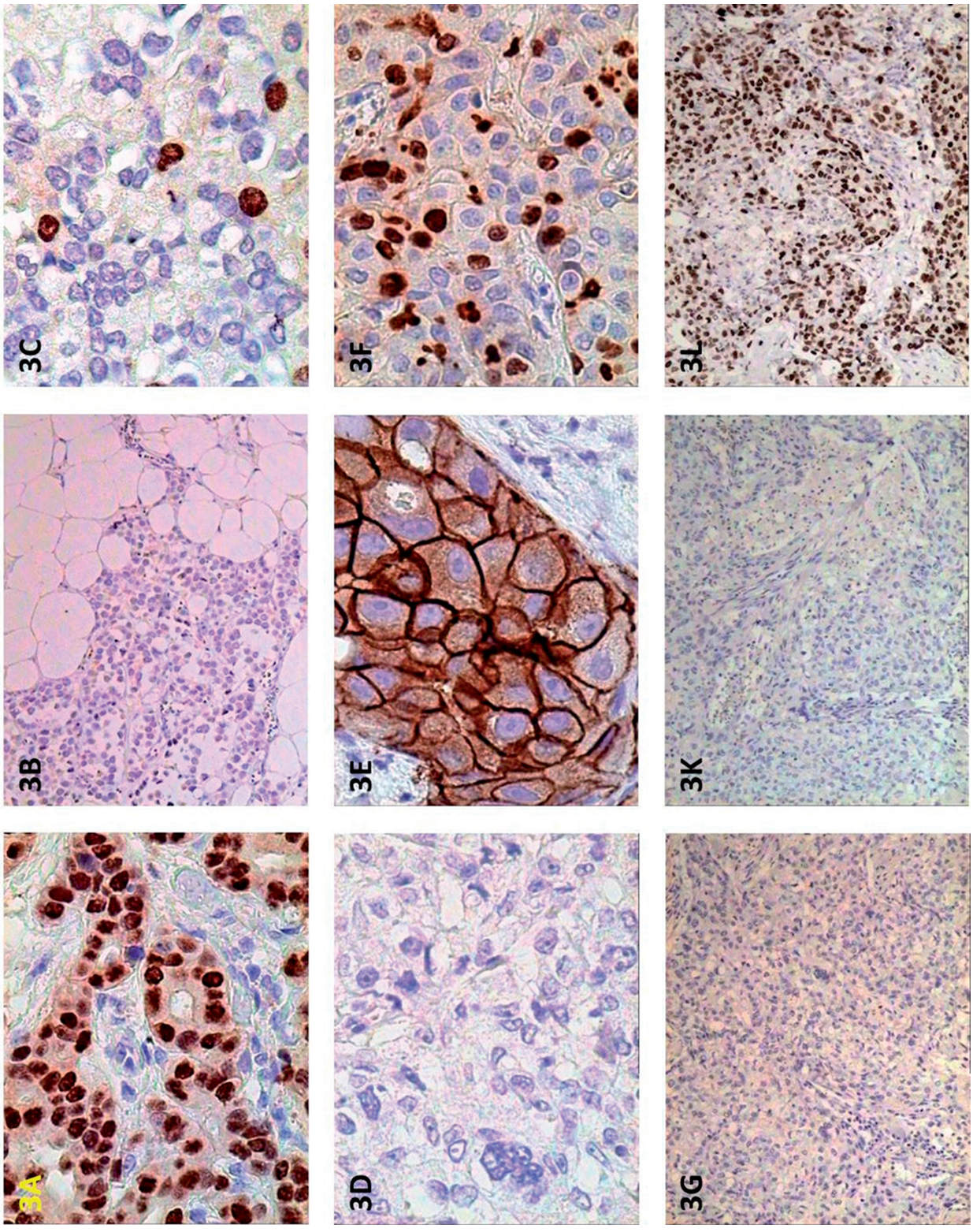

Fig. 3. Molecular subtypes of breast cancer. A-C, Luminal breast cancer. A, Estrogen receptor expression. B, Lack of HER2 protein. C. Low proliferation fraction. D-F, HER2 overexpressing breast cancer: D, lack of estrogen receptors; B, HER2 protein overexpression; C, Moderate proliferative fraction. G-L, triple negative breast cancer: G, lack of hormone receptors; K, lack of HER2 protein; L, high proliferative fraction. Immunoperoxidase, A, D and G, anti-estrogen receptor alpha; B, E and K, HercepTest; C, F and L, anti-Ki-67. OM 100x (B, G-L) and 400x (A, C-F).

The molecular subtype along with other factors as tumour size, lympho-vascular invasion, and age at diagnosis is found to influence the sentinel node positivity (Reyal *et al*., 2011). The molecular subtype thus interacts with metastatic process and is an evidence of up-to-date investigation of biological potential. It also correlates with the local tumour recurrence (Voduc *et al*., 2010), response to neoadjuvant systemic treatment (Rouzier *et al*., 2005), metastatic pattern (Gabos *et al.,* 2006) and survival (Weigelt *et al*., 2010).In addition, the molecular subtypes are related to different risk factors and differ by geographic distribution (Phipps *et al*., 2008). Thus, molecular subtyping of breast cancer identifies biologically different neoplastic processes with different clinical course and reaction to treatment.

Other molecular and biologic factors

The hot topics in breast cancer research include the wide and growing field of epigenetic research (Huang *et al*., 2011), investigation of microenvironment and breast adipocytes (Place *et al*., 2011; Tan *et al*., 2011) and studies of additional immunohistochemical factors. The studies of microenvironment concern myoepithelial cells, cancer-associated fibroblasts, matrix remodelling and infiltrating leukocytes as well as microenvironment of metastases in order to characterize prognosis and find new targets for treatment (Place *et al*., 2011). Novel molecular factors that might play role in breast cancer development, reveal prognosis and potentially become target for treatment, include fascin (Al-Alwan *et al.,* 2011), matrix metalloproteinase-1 (Bostrom *et al.,* 2011), cyclooxygenase-2 (Kang *et al.,* 2011), interleukins (Iliopoulos et al., 2011), p53 (Malhotra *et al.,* 2010), p27 (Wander et al., 2011) and apoptosis-related factors including Bcl-2 (Zaha and Lazar, 2012).

Molecular pathogenesis of breast cancer

Invasive breast cancer is preceded by several stages of *in situ* atypia, progressing to *in situ* cancer. There are at least 2 hypotheses of breast cancer origin: the sporadic clonal evolution model and the cancer stem cell model (Bombonati and Sgroi, 2011). The sporadic clonal evolution model describes the cancer development as accumulation of genetic and epigenetic changes in epithelial cells resulting in proliferation advantage. The stem cell model emphasize that normal breast stem cells accumulate the alterations due to prolonged lifetime of stem cells. The final pathogenetic way could incorporate elements from both models with accumulation of genetic mutations and epigenetic events in stem cells. It is also possible that progenitors of stem cell are the true cancer source; in this case the type of cancer would be dependent on the differentiation of progenitor cell (Nowell, 1976; Reya *et al*., 2001).

From pathologist's point of view, progression of malignancy to higher grade occasionally is evident. However, the genetic studies point towards association of several chromosomal aberrations with the grade (Roylance *et al*., 1999; Buerger *et al*., 1999). Loss of chromosome 16 is frequent in low-grade ductal and in classic lobular cancer, but rare in high-grade cancers. Other aberrations are described as well. The high-grade cancers are commonly characterised by loss of 13q, gain of chromosomal region 11q13, amplification of 17q12. *In situ* and invasive cancers share the aberrations by grade (Bombonati and Sgroi, 2011). Thus, low-grade and high-grade cancers seem to be more separated entities. It is estimated that 9% of high-grade cancers still develop from low-grade cancers (Allred *et al*., 2008; Natrajan *et al*., 2009). The further growth and metastatic spread are largely influenced by the molecular type. The most of molecular changes in the epithelium occur before invasion, but in stroma and microenvironment – during the transition from preinvasive to invasive cancer (Bombonati and Sgroi, 2011).

In conclusion, breast cancer is a heterogeneous group of tumours. In order to plan the treatment, histologic type and molecular subtype should be detected. To plan personalised treatment, knowledge about other, novel prognostic and predictive factors can be necessary.

Conflict of interest: None

REFERENCES

1. Al-Alwan M, Olabi S, Ghebeh H, Barhoush E, Tulbah A, Al-Tweigeri T, Ajarim D, Adra C. Fascin is a key regulator of breast cancer invasion that acts via the modification of metastasis-associated molecules // PLos One, 2011; 6(11):e27339
2. Allred DC, Wu Y, Mao S, Nagtegaal ID, Lee S, Perou CM, Mohsin SK, O'Connell P, Tsimelzon A, Medina D. Ductal carcinoma in situ and the emergence of diversity during breast cancer evolution // Clin Cancer Res, 2008; 14:370 – 378
3. Bombonati A, Sgroi DC. The molecular pathology of breast cancer progression // J Pathol, 2011; 223: 307 – 317
4. Bostrom P, Soderstrom M, Vahlberg T, Soderstrom KO, Roberts PJ, Carpen O, Hirsimaki P. MMP-1 expression has an independent prognostic value in breast cancer // BMC Cancer, 2011; 11:348
5. Buerger H, Otterback F, Simon R, Schafer KL, Poremba C, Diallo R, Brinkschmidt C, Dockhorn-Dworniczak B, Boecker W. Different genetic pathways in the evolution of invasive breast cancer are associated with distinct morphological subtypes // J Pathol, 1999; 189: 521 – 526
6. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, Millikan RC. Race, breast cancer subtypes, and survival in the Carolina breast cancer study // J Am Med Assoc, 2006; 295: 2492 – 2502
7. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, Watson M, Davies S, Bernard PS, Parker JS, Perou CM, Ellis MJ, Nielsen TO. Ki-67 index, HER2 status, and prognosis of patients with luminal B breast cancer // J Natl Cancer Inst, 2009; 101:736 – 750

8. Farmer P, Bonnefoi H, Becette V, Tubiana-Hulin M, Fumoleau P, Larsimont D, Macgrogan G, Bergh J, Cameron D, Goldstein D, Duss S, Nicoulaz AL, Brisken C, Fiche M, Delorenzi M, Iggo R. Identification of molecular apocrine breast tumours by microarray analysis // Oncogene, 2005; 24:4660 – 4671
9. Gabos Z, Sinha R, Hanson J, Chauhen N, Hugh J, Mackey JR, Abdulkarim B. Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breats cancer // J Clin Oncol, 2006; 24(36):5658 – 5663
10 Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ; Panel members. Strategies for subtypes – dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011 // Ann Oncol, 2011; 22(8):1736 – 1747
11. Guarneri V, Conte PF. Metastatic breast cancer: therapeutic options according to molecular subtypes and prior adjuvant therapy // The Oncologist, 2009; 14:645 – 656
12. Huang Y, Nayak S, Jankowitz R, Davidson NE, Oesterreich S. Epigenetics in breast cancer: what's new? // Breast Cancer Res, 2011; 13:225.
13. Iliopoulos D, Hirsch HA, Wang G, Struhl K. Inducible formation of breast cancer stem cell and their dynamic equilibrium with non-stem cancer cells via IL6 secretion // Proc Natl Acad Sci USA. 2011; 108(4):1397 – 1402
14. Kang JH, Song KH, Jeong KC, Kim S, Choi C, Lee CH, Oh SH. Involvement of Cox-2 in the metastatic potential of chemotherapy-resistant breast cancer cells // BMC Cancer, 2011; 11:334
15 Malhotra GK, Zhao X, Band H, Band V. Histological, molecular and functional subtypes of breast cancers // Cancer Biol Ther, 2010; 10(10):955 – 960
16. Natrajan R, Lambros MB, Geyer FC, Marchio C, tan DS, Vatcheva R, Shiu KK, Hungermann D, Rodriguez-Pinilla SM, Palacios J, Ashworth A, Buerger H, Reis-Filho JS. Loss of 16q in high grade breast cancer is associated with estrogen receptor status: evidence for progression in tumors with luminal phenotype? // Genes Chromosomes Cancer, 2009; 48:351 – 365
17. Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, Hu Z, Hernandez-Boussard T, Livasy C, Cowan D, Dressler L, Akslen LA, Ragaz J, Gown AM, Gilks CB, van de Rijn M, Perou CM. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma // Clin Cancer Res, 2004; 10: 5367 – 5374
18. Nielsen TO, Parker JS, Leung S. Voduc D, Ebbert M, Vickery T, Davies SR, Snider J, Stijleman IJ, Reed J, Cheang MC, Mardis ER, Perou CM, Bernard PS, Ellis MJ. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer // Clin Cancer Res, 2010; 16:5222 – 5232
19. Nowell PC. The clonal evolution of tumor cell populations // Science, 1976; 194:23 – 28
20. Parker JS, Mullins M, Cheang MC, Leung S, Voduc D, Vickery T, Davies S, Fauron C, He X, Hu Z, Quackenbush JF, Stijleman IJ, Palazzo J, Marron JS, Nobel AB, Mardis E, Nielsen TO, Ellis MJ, Perou CM, Bernard PS. Supervised risk predictor of breast cancer based on intrinsic subtypes // J Clin Oncol, 2009; 27:1160 – 1167
21. Peppercorn J, Perou CM, Carey LA. Molecular subtypes in breast cancer evaluation and management: divide and conguer // Cancer Invest, 2008; 26:1 – 10
22. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lonning PE, Borresen-Dale AL, Brown PO, Botstein D. Molecular portreits of human breast tumours // Nature, 2000; 406: 747 – 752
23. Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Reproductive and hormonal risk factors for postmenopausal luminal, HER2-overexpressing and triple-negative breast cancer // Cancer, 2008; 113(7):1521 – 1526
24. Place AE, Huh SJ, Polyak K. The microenvironment in breast cancer progression: biology and implications for treatment // Breast Cancer Res, 2011; 13:227
25. Prat A, Parker JS, Karginova O, Fan C, Livasy C, Herschkowith JI, He X, Perous CM. Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer // Breast cancer Res, 2010; 12:R68.
26. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells // Nature, 2001; 414:105 – 111
27. Reyal F, Rouzier R, Depont-Hazelzet B, Bollet MA, Pierga JY, Alran S, Salmon RJ, Fourchotte V, Vincent-Salomon A, Sastre-Garau X, Antoine M, Uzan S, Sigal-Zafrani B, De Rycke Y. The molecular subtype classification is a determinant of sentinel node positivity in early breast carcinoma // PLoS One, 2011; 6(5):e20297.
28. Roylance R, Gorman P, Harris W, Liebmann R, Barnes D, Hanby A, Sheer D. Comparative genomic hybridization of breast tumors stratified by histologic grade reveals new insights into the biological progression of breast cancer // Cancer Res, 1999; 59:1433 – 1463
29. Rozier R, Perou CM, Symmans WF, Ibrahim N, Cristofanilli M, Anderson K, Hess KR, Stec J, Ayers M, Wagner P, Morandi P, Fan C, Rabiul I, Ross JS, Hortobagyi GN, Pusztai L. Breast cancer molecular subtypes respond differently to preoperative chemotherapy // Clin Cancer Res, 2005; 11(16):5678 – 5685

30. Sorlie T. Molecular portraits of breast cancer: tumour subtypes as distinct disease entities // Eur J Cancer, 2004; 40:2667 – 2675
31. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Lonning PE, Borresen-Dale Al. Gene expression patterns of breast carcinomas distinguish tumour subclasses with clinical implications // Proc Natl Acad Sci USA, 2001; 98:10869 – 10874
32. Strehl JD, Wachter DL, Fasching PA, Beckmann MW, Hartmann A. Invasive breast cancer: Recognition of molecular subtypes // Breast Care, 2011; 6:258 – 264
33. Tan J, Buache E, Chenard MP, Dali-Youcef, Rio MC. Adipocyte is a non-trivial, dynamic partner of breast cancer cells // Int J Dev Biol, 2011; 55:851 – 859
34. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse // J Clin Oncol, 2010; 28(10):1684 – 1691
35. Zaha DC, Lazar E. Molecular characterization of apoptosis by the immunohistochemical evaluation of Bcl-2 in breast cancer // Rom J Morphol Embryol, 2012; 53(1): 155 – 160
36. Wander SA, Zhao D, Slingerland JM. P27: a barometer of signalind deregulation and potential predictor of response to targeted therapies // Clin Cancer Res, 2011; 17(1):12 – 18
37. Weigelt B, Mackay A, A'Hern R, Natrajan R, Tan DS, Dowsett M, Ashworth A, Reis-Filho JS. Breast cancer molecular profiling with single sample predictors: a retrospective analysis // Lancet Oncol, 2010; 11(4):339 – 349

ACKNOWLEDGEMENT

This work was supported by ESF project Nr. 2009/0230/1DP/1.1.1.2.0/09/APIA/VIAA/070.

Address:
Ilze Strumfa,
Department of Pathology,
Riga Stradins University,
Dzirciema Street 16,
Riga, LV-1007, Latvia
E-mail: Ilze.Strumfa@rsu.lv