neu (basal-like breast carcinomas). Mod Pathol 2007;20:1200–1207.
2 Jumppanen M, Gruvberger-Saal S, Kauraniemi P, *et al.* Basal-like phenotype is not associated with patient survival in estrogen-receptor-negative breast cancers. Breast Cancer Res 2007;9:R16.
3 Rouzier R, Perou CM, Symmans WF, *et al.* Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res 2005;11:5678–5685.
4 Sorlie T, Perou CM, Tibshirani R, *et al.* Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001;98:10869–10874.
5 Fan C, Oh DS, Wessels L, *et al.* Concordance among gene-expression-based predictors for breast cancer. N Engl J Med 2006;355:560–569.
6 Tan DS, Marchió C, Jones RL, *et al.* Triple negative breast cancer: molecular profiling and prognostic impact in adjuvant anthracycline-treated patients. Breast Cancer Res Treat 2007; epub ahead of print: doi: 10.1007/s10549-007-9756-8.
7 Rakha EA, El-Sayed ME, Green AR, *et al.* Prognostic markers in triple-negative breast cancer. Cancer 2007;109:25–32.
8 Tischkowitz M, Brunet JS, Begin LR, *et al.* Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC Cancer 2007; 7:134.
9 Nielsen TO, Hsu FD, Jensen K, *et al.* Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin Cancer Res 2004;10:5367–5374.
10 Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: a critical review. J Clin Oncol 2008 (in press).
11 Savage K, Lambros MB, Robertson D, *et al.* Caveolin 1 is overexpressed and amplified in a subset of basal-like and metaplastic breast carcinomas: a morphologic, ultrastructural, immunohistochemical, and *in situ* hybridization analysis. Clin Cancer Res 2007;13:90–101.
12 Rakha EA, Putti TC, Abd El-Rehim DM, *et al.* Morphological and immunophenotypic analysis of breast carcinomas with basal and myoepithelial differentiation. J Pathol 2006;208:495–506.

Modern Pathology (2008) **21,** 1061–1062; doi:10.1038/modpathol.2008.68

In reply: In reply to the Letter to the Editor by Drs Rakha, Ellis and Reis-Filho, regarding our article,[1] we would like to clarify the following:

Triple-negative (ER/PR/HER2-negative) breast cancer constitutes more than one entity with heterogeneous and poorly understood growth and invasive mechanisms. Despite concordance between histopathology, immunohistochemistry and cDNA analysis, a pragmatic approach should be considered for identification of these tumors for treatment.[2] We agree that negativity for ER/PR/HER2 is not an obligated criteria to classify breast tumors as basal-like carcinomas, but for the purpose of our study, we only selected the triple-negatives tumors for analyzing several biological markers. The use of both terms indistinctly throughout the text might have led to some confusion.

From a histopathological point of view, it is true that basal-like breast carcinomas are heterogeneous groups of high-grade invasive ductal neoplasms (NOS), which also include most of the myoepithelial, medullary, adenoid cystic, metaplastic and spindle cell carcinomas.[3] Apparently, they are not specific markers to classify these tumors. Recently, it has been stated that the immunohistochemical pattern that best defines basal-like breast carcinomas is the triple negativity in association with the positivity for EGFR and/or basal cytokeratins (CKs) (ie, CK5/6, CK14 and CK17).[4] Few investigators have analyzed all three CKs together, as we did. Nevertheless, in our cases, we did not find any statistical correlation between expression of several CKs (data not included in our paper). Furthermore, how basal CK expression contributes to the adverse prognosis of these tumors is currently unknown. Among our triple-negative cases with myoepithelial differentiation, we also observed a heterogeneous pattern of CK expression. Moreover, positive S100 expression was observed more frequently than SMA expression, and interestingly, in other studies, SMA expression was detected more frequently than p63.[3] It means that the characterization of these neoplasms is still blurry.

The level of EGFR expression has been revealed as an independent predictor of tumor response to radiation therapy.[5] The contribution of our immunohistochemical study in this field is that, in fact, in triple-negative breast carcinomas, several growth-factor receptors (ie, EGFR, IGF1R, PDGFRá, and so on) are involved, and therefore, they could explain the aggressive clinical behavior in some cases.

Other markers, such as p53 overexpression, have been considered a common marker of basal-like breast carcinoma,[6] but it has also been detected in 11.3% of ER-positive breast carcinomas.[7] Therefore, current evidence is still insufficient to support the routine analysis of p53 in clinical practice.[8]

Dendrograms of expression profiling/hierarchical clustering analysis are not available for most institutions. Of note, comparative studies with different gene sets for breast cancer diagnosis achieved 77–81% agreement for outcome classification,[9] as with immunohistochemistry and conventional histopathology.

In summary, the data reviewed above indicate that characterization and/or classification of these neoplasms is still undergoing investigation. Therefore, more research should be conducted in this field to define the underlying mechanisms, which in turn will provide better understanding of breast neoplasms for more accurate patient treatment.

Enrique Lerma and Gloria Peiro
Department of Pathology, Hospital Santa Creu i Sant Pau, Barcelona, Spain

References

1 Lerma E, Peiro G, Ramon T, *et al.* Immunohistochemical heterogeneity of breast carcinomas negative for estrogen receptors, progesterone receptors and Her2/neu (basal-like breast carcinomas). Mod Pathol 2007;20:1200–1207.
2 Haffty BG, Yang Q, Reiss M, *et al.* Locoregional relapse and distant metastasis in conservative managed triple negative early stage breast cancer. J Clin Oncol 2006;24:5652–5657.
3 Rakha EA, Putti TC, Abd El-Rehim DM, *et al.* Morphological and immunophenotypic analysis of breast carcinomas with basal and myoepithelial differentiation. J Pathol 2006;208:495–506.
4 Tischkowitz M, Brunet JS, Bégin LR, *et al.* Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC Cancer 2007;7:134; doi:I0. 1186/1471–2407/7/134.
5 Riesterer O, Milas L, Ang KK. Use of molecular biomarkers for predicting the response to radiotherapy with or without chemotherapy. J Clin Oncol 2007;25: 4075–4083.
6 Rakha EA, El-Sayed ME, Green AR, *et al.* Prognostic markers in triple-negative breast cancer. Cancer 2007; 109:25–32.
7 Olivier M, Langerod A, Carrieri P, *et al.* The clinical value of somatic TP53 gene mutations in 1794 patients with breast carcinoma. Clin Cancer Res 2006; 12:1157–1167.
8 Harris L, Fritsche H, Mennel R, *et al.* American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 2007;25:5287–5312.
9 Fan C, Oh DS, Wessels L, *et al.* Concordance among gene-expression-based predictors for breast cancer. N Engl J Med 2006;355:560–569.