Serum autoantibodies to breast cancer associated antigens reflect tumor biology: an opportunity for early detection & prevention?

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Background

Autoantibodies (AABs) are produced as an immune response to abnormal ('non-self') tumor-associated antigens (TAA). Previous studies have reported that AABs can be measured in the blood long before cancers are presently diagnosed, e.g. up to 4 years before screening mammography identified breast cancers[1] and up to 5 years before screening CT detected lung cancers[2]. *Early*CDT®-Lung is currently available as an aid to early detection of lung cancer in individuals at high risk of lung cancer (eg heavy smoking history) and measures a panel of seven AABs, some to generic cancer antigens and also some to more lung cancer specific antigens [3,4].

Aims

The aim of this study was to investigate AABs to 4 generic cancer antigens to evaluate if the levels reflected different biology in primary breast tumors.

Methods

770 patients presented with primary breast cancer (PBC) to three centres (Nottingham, UK n=323; Munich, Germany n=320; Oklahoma, USA n=127); the median ages and ranges were 61 (26-82), 61 (20-88) & 65 (54-84) years, respectively. All had serum samples taken post-diagnosis and pre-treatment. The tumors were well characterized for histological grade, estrogen receptor (ER), progesterone receptor (PgR) and HER2 status. Serum samples were tested for AABs to four generic cancer antigens(Ags) (p53, SOX2, NY-ESO-1 and Annexin1) originally part of Oncimmune's *Early*CDT®-Lung assay. The AABs were measured by ELISA on the Oncimmune platform, and the *Early*CDT®-Lung cut-offs were used to determine positivity.

Results

131/770 (17%) of PBCs showed elevated AAB levels to one or more of the limited panel of four generic antigens. Positivity for each AAB was correlated with histological grade, ER, PgR and HER2 status. The result, (similar for each of the three centres) were combined (Table 1).

	High Grade	ER positive	PgR positive	Her2 positive
p53	8/15 (53%)	6/16 (38%)	4/16 (25%)	10/16 (63%)
NY-ESO-1	17/19 (89%)	7/19 (37%)	7/19 (37%)	3/19 (16%)
SOX2	18/75 (24%)	65/75 (86%)	54/74 (73%)	17/74 (23%)
Annexin 1	9/22 (41%)	17/23 (74%)	13/23 (57%)	4/22 (18%)

Table 1: Antigen specific AAB positivity in breast cancer patients according to the histopathological features of the tumor.

p53 AAB positive cancers tended to be higher grade (grade 2/3) and be associated with hormone receptor negativity and HER2 positivity; the most common single biological phenotype being ER negative/PgR negative and HER2 positive.

NY-ESO-1 positive tumors were almost all high grade (grade 3) with the majority hormone receptor and HER2 negative; the most single common phenotype being triple negative

SOX2 positive cancers tended to have a hormone sensitive phenotype (i.e., hormone receptor positive and HER2 negative); the most common single phenotype being ER positive/PgR positive/HER2 negative.

Annexin1 positive cancers also tended to have a hormone sensitive phenotype as well as HER2 negative; the most common single phenotype being ER positive/PgR positive/HER2 negative.

These data are demonstrated graphically in Figure 1.

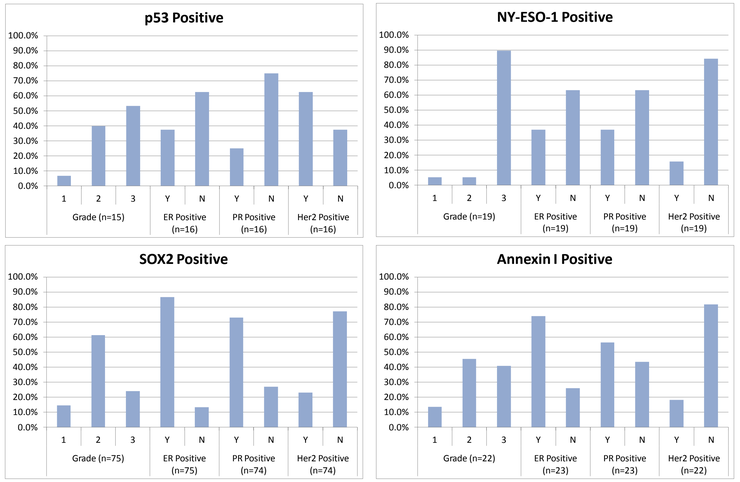

Fig1: AAB responses according to histopathological features of the tumor

The pattern was statistically different for the four AABs (p<0.001). The autoantibody profile for ER positive tumors was not statistically different from PgR positive tumors.

Conclusions

1) The 4 specific AABs measured are associated with different tumor biology.
2) Extending this finding to AABs to other cancer antigens could lead in the future to using immuno-biomarkers as a serum-based method of profiling tumors.

References

1) Chapman *et al.* (2005) Autoantibodies in early breast cancer. *J Clin Oncol,* 18: 868-873. 2) Zhong *et al.* (2006) Profiling tumor-associated antibodies for early detection of NSCLC. *J Thor Oncol,* 1:513-9 3) Murray *et al.* (2010) Technical validation of an autoantibody test for lung cancer. *Ann Oncol,* 21:1687-1693. 4) Boyle *et al.* (2011) Clinical validation of an autoantibody test for lung cancer. *Ann Oncol* 22: 383-9.