AUTOANTIBODIES IN BREAST CANCER:
their use as an aid to early diagnosis

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SUMMARY

Autoantibodies against one or more tumor-associated antigens in serum appears to indicate the presence of early stage breast cancers.

Autoantibody assays against a panel of antigens could be used in conjunction with mammography in the detection and diagnosis of early primary breast cancer, especially in younger women at increased risk of breast cancer where mammography is known to have reduced sensitivity and specificity.

INTRODUCTION

Breast cancer accounts for 22% of all cancers diagnosed in women worldwide with the risk of developing breast cancer increasing with age.

Early detection of small breast cancers significantly improves a woman's chances of survival and if breast cancer is diagnosed and treated while it is still confined to the breast the cure rate can approach 100%.

Screening mammography is far from perfect in terms of uptake by women, sensitivity of cancer detection (70-80% across all age groups) and specificity, with a recall rate of approximately 5-10%. In only 5-10% of those women recalled for additional testing will a breast cancer be found.

Breast cancer is a heterogeneous disease with tumors expressing a variety of aberrant proteins. Current blood tests that identify circulating tumor antigens are elevated most commonly in patients with metastatic disease and appear to reflect tumor bulk. They are too insensitive to be used for the screening and early diagnosis of primary breast cancers.

Autoantibodies produced against such tumor-associated antigens may provide an *in vivo* amplification of an early carcinogenic signal and therefore may allow earlier detection of cancer than current methods allow.

METHODS

Autoantibodies to p53, c-myc, HER2 (ECD), NY-ESO, BRCA1, BRCA2 & MUC1 were measured using indirect ELISAs in 97 newly diagnosed primary invasive breast cancers (PBC), 40 DCIS and 96 normal individuals.

	PBC	DCIS
Number	97	40
Mean Age (range) years	59 (30-82)	59 (37-86)
Mean size (range) mm	17 (0.5-47)	27 (3-110)
Size (n) <2 / 2-5/ >5cm	64 / 33 / 0	17 / 14 / 9
Invasive Ductal : Other	66 : 31	
Grade (% total)	**1 2 3** 12 52 36	Low-----High 10 28 62
Lymph Node +ve	30%	
ER +ve	81%	
Vascular Invasion +ve	26%	

Serum samples were run in triplicate and repeated 3-5 times.

REFERENCES

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Molina R et al. *Tumor Biol* 2005; **26:** 281-93.

RESULTS

Individual and panel autoantibody sensitivity by grade.
Percentage positivity for each antigen is shown. Positivity defined as a OD value > mean+2SD of normal population. Detection of autoantibodies to BRCA1 afforded no diagnostic potential so was not included in the panel analysis

PBC Grade	p53	c-myc	NYESO	BRCA1	BRCA2	HER2	MUC1	PANEL
G1	9%	0%	18%	0%	36%	0%	9%	**55%**
G2	32%	14%	20%	10%	36%	20%	24%	**62%**
G3	15%	15%	39%	9%	30%	18%	18%	**73%**
ALL	**24%**	**13%**	**26%**	**8%**	**34%**	**18%**	**20%**	**64%**
DCIS Grade	p53	c-myc	NYESO	BRCA1	BRCA2	HER2	MUC1	PANEL
Low	0%	0%	20%	20%	0%	0%	0%	20%
Int	15%	15%	8%	0%	15%	23%	23%	62%
High	18%	5%	5%	0%	32%	9%	30%	41%
ALL	**15%**	**8%**	**8%**	**3%**	**23%**	**13%**	**23%**	**45%**
Specificity	96%	97%	94%	91%	92%	94%	98%	85%

Elevated levels of autoantibodies were seen to at least 1/6 antigens in 64% of PBC sera and 45% of patients with DCIS at a specificity of 85%. Reproducibility of the individual assays was 90-97%.

Autoantibody Panel sensitivity.
Percentage of each patient group positive for 1 or more autoantibodies.
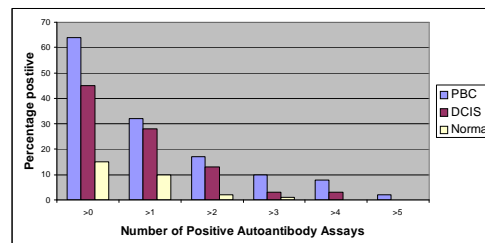
Autoantibody sensitivity by age; lymph node status and detection methodology.
Percentage positivity for each antigen is shown.

Age (years)	PBC -n	PBC +ve	DCIS -n	DCIS +ve
<50	21	48%	6	33%
50-59	30	57%	14	43%
60-69	27	74%	16	50%
>70	19	79%	4	75%

PBC	% Positivity
Screen Detected	67
Symptomatic Detection	62
Lymph Node +ve	70
Lymph Node -ve	54

No significant differences were seen when patients were sub-divided by age; lymph node status; detection methodology; tumor size or histological grade.

DISCUSSION

This study demonstrates that an autoantibody panel ELISA system can be used to reproducibly identify 64% of women with early invasive primary breast cancer, and 45% of women with DCIS, independent of the clinical or histological features of the tumor.

Autoantibody assays may have a significant role to play in the future of early breast cancer diagnosis.