The oestrogen receptor–negative/progesterone receptor-positive (ER-/PR+) breast tumour: A biological entity or a technical artefact?

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To the Editor: A recent study by Rakha *et al.,* (1) shows that breast tumours with single hormonal receptor positivity are biologically and clinically distinct groups and particularly that Oestrogen receptor (ER)-negative/Progesterone receptor (PR)-positive tumours exhibit more aggressive behavioural characteristics than double receptor positive tumours. However, there is also an increasingly prevalent opinion, that the ER-negative/PR-positive phenotype does not exist and that the ER-negativity in these cases is due to inadequate tissue fixation or technical failure of the immunohistochemical assay (2, 3, 4).

This is an important dichotomy to resolve since if ER-/PR+ tumours simply represent an artefact of the method of assessment then they are essentially positive for both the receptors, which may have implications for how these patients are managed. In order to investigate this issue, we reviewed data from a previous study, in which we had accumulated data on ER/PR phenotype expression in a large cohort of patients tested in 42 laboratories (5). In this study of 4,053 breast tumours, a sizeable number (n=131) were of the ER-/PR+ phenotype which, unlike other studies with lower numbers of cases, allowed us to statistically test the distribution of this phenotype in stratified age groupings (Table 1). We found that the ER-/PR+ phenotype occurs over twice as frequently in the <51 year patient age group than it does in the >50 year patient age group (Table 2 & Figure 1). This suggests that the ER-/PR+ phenotype is a biological entity. In order to further validate this possibility and exclude any methodological factor, we restricted the analysis to those results achieved from 16 laboratories that were proven to have reliable immunohistochemical assays of high sensitivity, due to their optimal performance in a national quality assurance program (5). These laboratories used antibodies and reagents similar and in some cases identical to those used by Rakha *et al.,* (1) and Nadji *et al.,* (2). The results proved very similar to those derived from the full set of data; with the ER-/PR+ phenotype occurring twice as frequently in the <51 age group than in the >50 age group (Figure 1 and Table 2). It appears therefore that the ER-/PR+ breast carcinoma represents a distinct biological phenotype; if it were not and it was due to false negative ER results caused by technical failure, as purported by De Maeyer *et al.,* (4) and by Nadji (3), the phenotype would occur with random frequency across all age groups.

Table 1. The ER & PR status of 4,053 invasive breast carcinomas with respect to patient age (5).

Age in years	*ER+ve, PR+ve*	*ER-ve, PR-ve*	*ER+ve, PR-ve*	*ER-ve, PR+ve*	*Total no in each age group*
21-30	18(45.0%)	17(42.5%)	3(7.5%)	2(5.0%)	***40(1.0%)***
31-40	134(45.9%)	97(33.2%)	45(15.4%)	16(5.5%)	***292(7.2%)***
41-45	195(57.9%)	88(26.1%)	35(10.4%)	19(5.6%)	***337(8.3%)***
46-50	319(58.6%)	116(21.3%)	83(15.3%)	26(4.8%)	***544(13.4%)***
51-55	278(53.5%)	114(21.9%)	112(21.5%)	16(3.1%)	***520(12.8%)***
56-60	239(51.0%)	102(21.8%)	111(23.7%)	16(3.4%)	***468(11.6%)***
61-65	271(55.3%)	98(20.0%)	113(23.1%)	8(1.6%)	***490(12.1%)***
66-70	251(57.2%)	85(19.4%)	94(21.4%)	9(2.1%)	***439(10.8%)***
71-75	194(57.6%)	60(17.8%)	76(22.6%)	7(2.1%)	***337(8.3%)***
>75	323(55.1%)	119(20.3%)	132(22.5%)	12(2.1%)	***586(14.5%)***
Total (receptor status)	***2222(54.8%)***	***896(22.1%)***	***804(19.8%)***	***131(3.2%)***	***4053(100%)***

Figure 1. The mean frequency of occurrence of invasive breast tumours with the ER-negative PR-positive phenotype in patients of <51 and >50 years of age.

KEY: Frequency in (a): A series of 4,053 breast tumours from 42 laboratories,
(b) A sub-series of 1,985 breast tumours from 16 laboratories with high assay sensitivity for ER & PR.

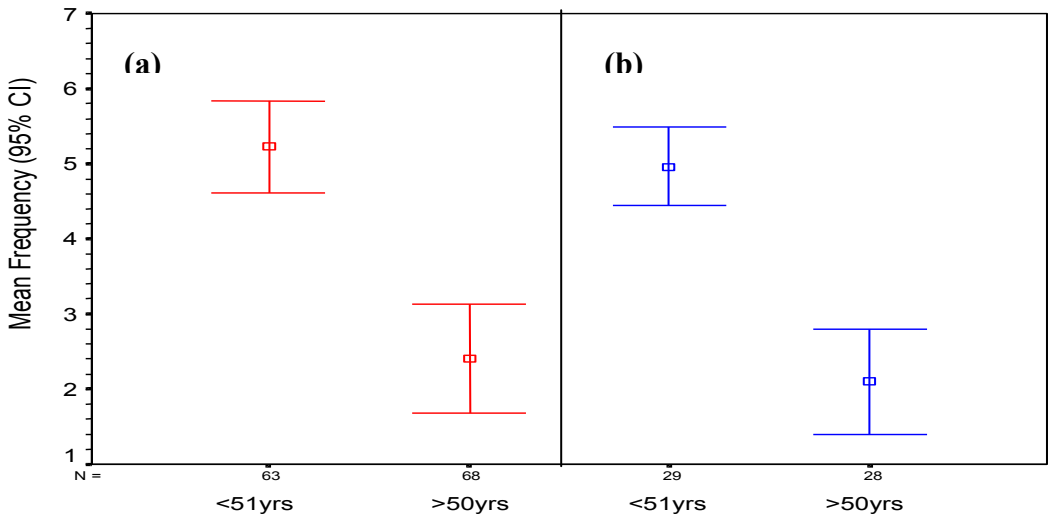

Table 2. The frequency of invasive breast tumours with the ER-negative PR-positive phenotype in patients of <51 years and >50 years of age, in 4,053 cases (a) and in a sub-set of 1, 985 tumours from laboratories shown to have high assay sensitivity for ER and PR (b).

Series	*Er-vePr+ve*	*Mean frequency (%)*		*Mann-Whitney U*	*p (2-tailed)*
	n	*<51yrs*	*>50yrs*		
(a) 4,053 tumours	131	5.2 (95% CI 4.6-5.8)	2.4 (95% CI 1.7-3.1)	0.000	0.010
(b) 1,985 tumours	57	5.0(95% CI 4.4-5.5)	2.1 (95% CI 1.4-2.8)	0.000	0.020

We appreciate that the cut-points that define a positive and negative result for ER and PR have lowered in recent years, in some instances to one in which as little as 1% of receptors present are considered to be a positive result, with respect to the patients likely response to hormonal therapy (6). In addition, a recent study by Dabbs *et al.,* (7) has clearly demonstrated that even when utilizing optimally fixed tissues and any level of nuclear immunohistochemical staining of invasive tumour cells as a positive result, the ER-/PR+ pheonotype is still retained as an entity in approximately 5% of breast tumours. These studies taken together provide further evidence that ER-/PR+ is not an artefact of fixation or due to the use of a lower threshold to define ER receptor positivity.

The evidence presented confirms that there is undetectable expression of ER in the tumours of at least a small proportion (2-5%) of breast cancer patients that have relatively high levels of PR expression. In addition it shows that the ER-/PR+ phenotype occurs on average twice as frequently in relatively younger patients (<51 years). These findings taken together with the fact that these patients have worse outcome than unequivocal double receptor positive cases clearly indicate the need to test all ER-negative tumours for their PR status even though the ER-/PR+ phenotype overall represents a small proportion of all breast cancers.

References

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