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A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases ☆

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Abstract ***Background:*** The discordance in oestrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) status between primary and recurrent breast cancer is being intensively investigated and a large amount of data have been produced. However, results from different studies are heterogeneous and often conflicting. To highlight this issue, a meta-analysis of published data was performed.

Methods: A literature search was performed using Medline, and all the studies published from 1983 to 2011 comparing changes in ER, PgR and/or HER2 status in patients with matched breast primary and recurrent tumours were included. We used random-effects models to estimate pooled discordance proportions.

Results: We selected 48 articles, mostly reporting retrospective studies. Thirty-three, 24 and 31 articles were focused on ER, PgR and HER2 changes, respectively. A total of 4200, 2739 and 2987 tumours were evaluated for ER, PgR and HER2 discordance, respectively. The heterogeneity between study-specific discordance proportions was high for ER ($I^2 = 91\%$,

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$p < 0.0001$), PgR ($I^2 = 79\%$, $p < 0.0001$) and HER2 ($I^2 = 77\%$, $p < 0.0001$). Pooled discordance proportions were 20% (95% confidence interval (CI): 16–35%) for ER, 33% (95% CI: 29–38%) for PgR and 8% (95% CI: 6–10%) for HER2. Pooled proportions of tumours shifting from positive to negative and from negative to positive were 24% and 14% for ER ($p = 0.0183$), respectively. The same figures were 46% and 15% for PgR ($p < 0.0001$), and 13% and 5% for HER2 ($p = 0.0004$).

Conclusion: Our findings strengthen the concept that changes in receptor expression may occur during the natural history of breast cancer, suggesting clinical implications and a possible impact on treatment choice.

1. Introduction

Since the late 70s, and especially during the last decade, the occurrence of phenotype discordance in hormone receptor (oestrogen receptor (ER) and progesterone receptor (PgR)) and human epidermal growth factor receptor 2 (HER2) status between primary and recurrent breast cancer has been repeatedly reported [1,2]. This evidence sprang mostly from retrospective analyses investigating ER, PgR and HER2 in heterogeneous sites of relapses, including local recurrences, regional lymph nodes and distant metastases, although a few studies prospectively evaluated the impact of phenotype discordance in patients' management (e.g. treatment planning) and survival.

Reassessing the biological features of disease is not currently considered mandatory, and has been largely individualised, although recent international guidelines encourage to perform biopsy of metastatic sites, mostly when they represent the first recurrence of disease and/or ER/PgR/HER2 status is unknown or originally negative [National Comprehensive Cancer Network (NCCN) guidelines 2012].

In order to shed light to this debated topic, we performed a meta-analysis of the studies evaluating the discordance rate in ER, PgR and HER2 status between primary tumour and corresponding relapse.

2. Methods

2.1. Selection of studies

A literature search was performed through the Medical Literature Analysis and Retrieval System Online (MEDLINE) database (up to December 2011, including three studies e-pub ahead of print in 2011 and published in 2012), using the medical subject headings terms 'Breast cancer' and 'Recurrence', or 'Neoplasm Metastasis' and 'Receptors, Oestrogen' or 'Receptors, Progesterone' or 'Genes, erbB-2/HER2'. Moreover, the reference lists of the papers of interest was manually screened to ensure sensitivity of the search strategy and to identify additional relevant studies. We limited our search to studies published in English.

Studies that reported changes in hormonal receptors (ER and PgR) and/or HER2 status in patients with matched primary breast tumour and recurrence tissues, published as original articles, were selected. Abstracts, letters, reviews and meta-analyses were not considered.

2.2. Data collection

The selected publications were independently reviewed by two of the authors (D.D. and G.A.) to determine the eligibility of each article in the meta-analysis. Doubts or disagreement was resolved by consensus among the two investigators. The following details were extracted: total number of patients evaluated, sites of relapse and ER, PgR and HER2 discordance rate. Whenever reported, we also recorded the prevalence of patients whose ER, PgR and HER2 status shifted from positive to negative and *vice versa*. The technique used to define the HER2 status, immunohistochemistry (IHC) and/or Fluorescent In Situ Hybridisation (FISH) was also registered.

2.3. Statistical analysis

The proportion of ER, PgR and HER2 changes with exact 95% confidence intervals (CIs) was calculated for each study. The Freeman–Tukey double arcsine transformation was used for the calculation of pooled estimates and corresponding 95% CIs [3,4]. Random-effects pooled estimates were calculated in order to take into account heterogeneity between estimates [5].

Statistical heterogeneity among studies was evaluated using the chi-square test statistic and was measured using the I^2 statistic, which is the proportion of total variation contributed by between-study variance tao-squared (τ^2) [6].

Chi-square statistics was used to test for differences of summary estimates among subgroups [7]. Publication bias was evaluated using funnel plots and the asymmetry test developed by Egger and colleagues [8]. All analyses were carried out with the SAS software (SAS Institute, Cary, NC) and the R software (http://cran.r-project.org/) with package 'meta'. All the reported P values were two sided.

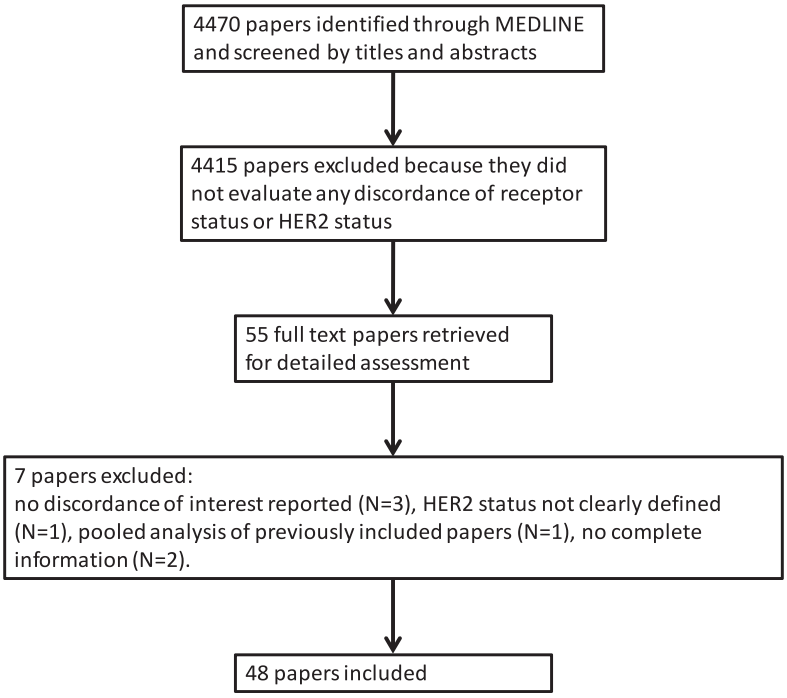


Fig. 1. Flow-chart of selection strategy.

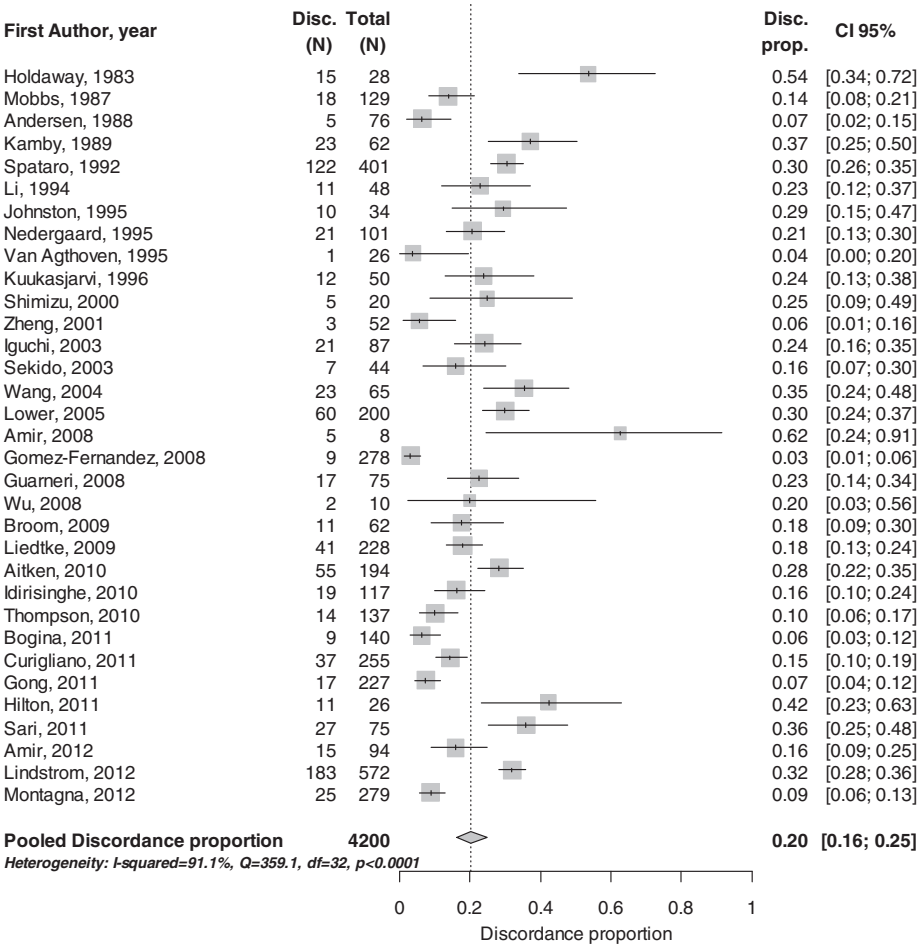


Fig. 2. Forest plot for proportion of discordance oestrogen receptor (ER).

Table 1
Pooled proportion of discordance oestrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) by relapse site.

Any discordance	LR		DM		*p*-Value*
	N	Pooled (confidence interval (CI) 95%)	*N*	Pooled (CI 95%)	
ER	15	0.16 (0.11–0.22)	15	0.23 (0.16; 0.30)	0.13
PgR	9	0.26 (0.21–0.32)	12	0.41 (0.37; 0.45)	<0.0001
HER2	12	0.06 (0.03–0.09)	18	0.10 (0.07; 0.14)	0.039

LR: loco-regional, DM: distant metastases.
* *p*-Value of test of heterogeneity between groups.

3. Results

Forty-eight studies were identified (Fig. 1, [9–56]) and their main characteristics are reported in the Appendix. ER, PgR and HER2 status in the primary tumour and corresponding relapses were available in 33, 24 and 31 studies, respectively. The discordance rate was assessed in 4200 patients for ER, 2987 patients for HER2 and 2739 patients for PgR. There was no evidence for publication bias for ER, PgR and HER2 (Egger's test: $p = 0.17$, $p = 0.55$ and $p = 0.38$, respectively. Supplementary Fig. 1).

3.1. Evaluation of ER

Fig. 2 shows the discordance proportions reported for ER in each study included in the analysis. The heterogeneity between proportions ranged from 3% [37] to 62% [44] ($I^2 = 91\%$, $\tau^2 = 0.08$, $p < 0.0001$). The meta-analytic pooled discordance proportion was 20% (95% CI: 16–35%). Stratified analysis performed according to the site of relapse revealed similar pooled discordance proportions across strata ($p = 0.13$, Table 1). The pooled discordance proportions in prospective and retrospective studies were respectively 29% (95% CI: 15–46%) and 19% (95% CI: 15–24%) ($p = 0.23$). Fig. 3 shows the proportions of patients whose tumour ER status changed from positive to negative (Fig. 3A), and from negative to positive (Fig. 3B). The pooled proportion of negative and positive conversion was 24% (95% CI: 9–20%) and 14% (95% CI: 9–20%), respectively ($p = 0.02$).

3.2. Evaluation of PgR

Fig. 4 shows the discordance proportions reported for PgR in each study included in the analysis.

The heterogeneity between proportions ranged from 12% [17] to 54% [47] ($I^2 = 79\%$, $\tau^2 = 0.04$, $p < 0.0001$). The meta-analytic pooled discordance proportion was 33% (95% CI: 29–38%). Stratified analysis performed according to the site of relapse revealed different pooled discordance proportions across strata ($p < 0.0001$, Table 1). The highest pooled discordance proportion was 41% (95% CI: 37–45%) in studies comparing primary tumours and distant metastases, while the same figure was 26% (95% CI: 21–32%) in studies comparing primary tumours and loco-regional relapse. The pooled discordance proportions in prospective and retrospective studies were respectively 37% (95% CI: 25–50%) and 33% (95% CI: 28–37%) ($p = 0.49$).

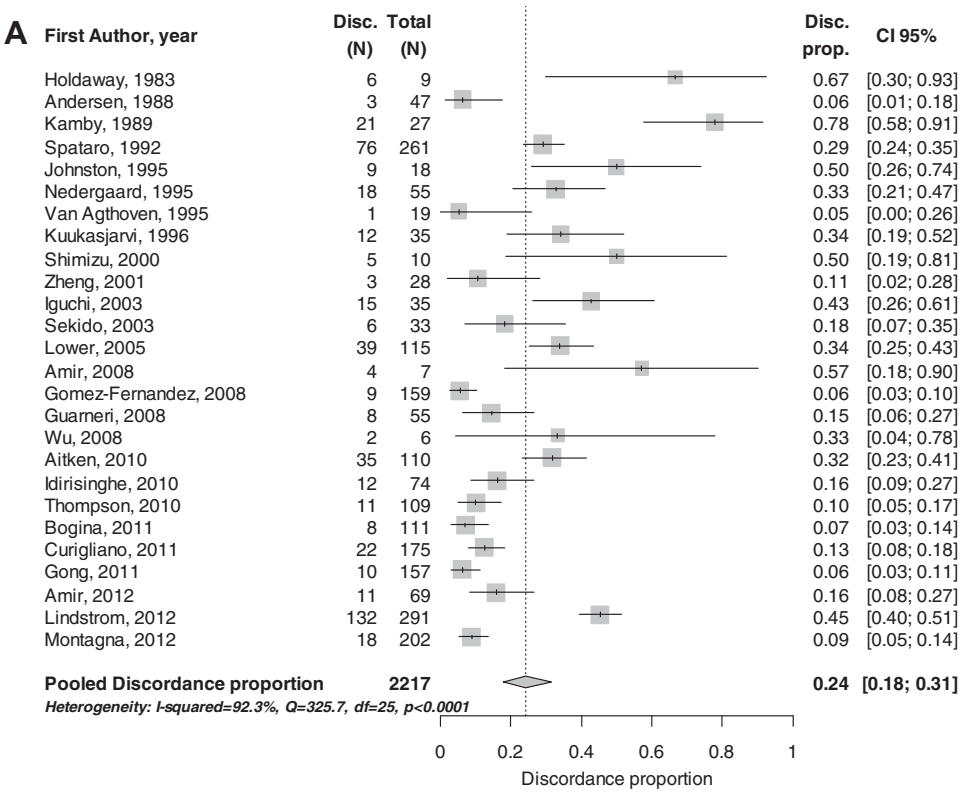
Fig. 5 shows the proportions of patients whose tumour PgR status changed from positive to negative (Fig. 5A), and from negative to positive (Fig. 5B). The pooled proportion of negative and positive conversion was 46% (95% CI: 37–55%) and 15% (95% CI: 12–17%), respectively ($p < 0.0001$).

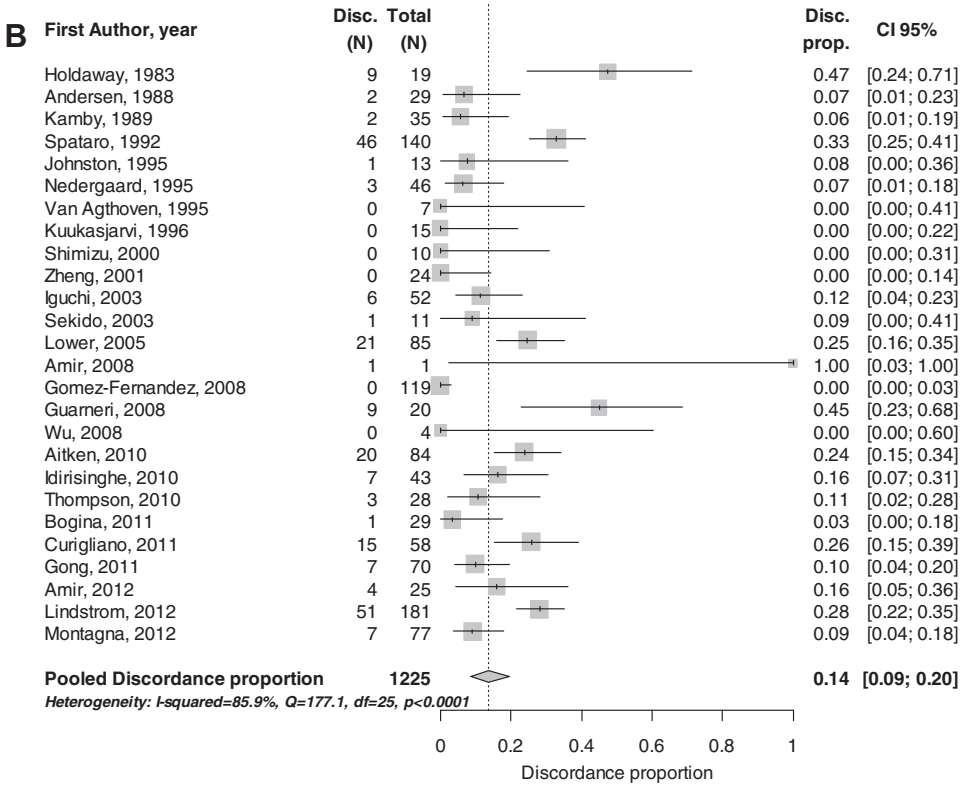
3.3. Evaluation of HER2

Fig. 6 shows the discordance proportions reported for HER2 in each study included in the analysis. The heterogeneity between proportions ranged from 0% [13,20,22,29] to 24% [30] ($I^2 = 77\%$, $\tau^2 = 0.03$, $p < 0.0001$).

The meta-analytic pooled discordance proportion was 8% (95% CI: 6–10%). Stratified analysis conducted according to the site of relapse revealed different pooled discordance proportions across strata: in particular, the pooled discordance proportion with respect to the primary tumour was 10% for distant metastases (95% CI: 7–14%), and 6% for loco-regional relapse (95% CI: 3–9%) ($p = 0.039$, Table 1). Different pooled discordance proportions across strata were found when the technique used to define HER2 status was taken into account: the pooled discordance proportion was 10% in studies using IHC and FISH (95% CI: 7–12%) and 5% (95% CI: 2–8%) in studies using IHC only ($p = 0.02$). The pooled discordance proportions in prospective and retrospective studies were respectively 10% (95% CI: 4–18%) and 8% (95% CI: 6–10%) ($p = 0.61$).

Fig. 7 shows the proportions of patients whose HER2 status changed from positive to negative (Fig. 7A), and from negative to positive (Fig. 7B). The pooled proportion of negative and positive conversion was 13% (95% CI: 9–18%) and 5% (95% CI: 4–8%) ($p = 0.0004$). In particular, the pooled proportion of negative and positive conversion was 15% (95% CI: 10–21%) and 7% (95% CI: 5–10%) in studies using IHC and FISH, respectively ($p = 0.04$), and 8% (95% CI: 4–13%) and 2% (95% CI: 1–4%) in studies using IHC only, respectively ($p = 0.001$).





p-value Between negative conversion and positive conversion =0.0183.

Fig. 3. (A) Forest plot for proportion of negative conversion oestrogen receptor (ER). (B) Forest plot for proportion of positive conversion ER.

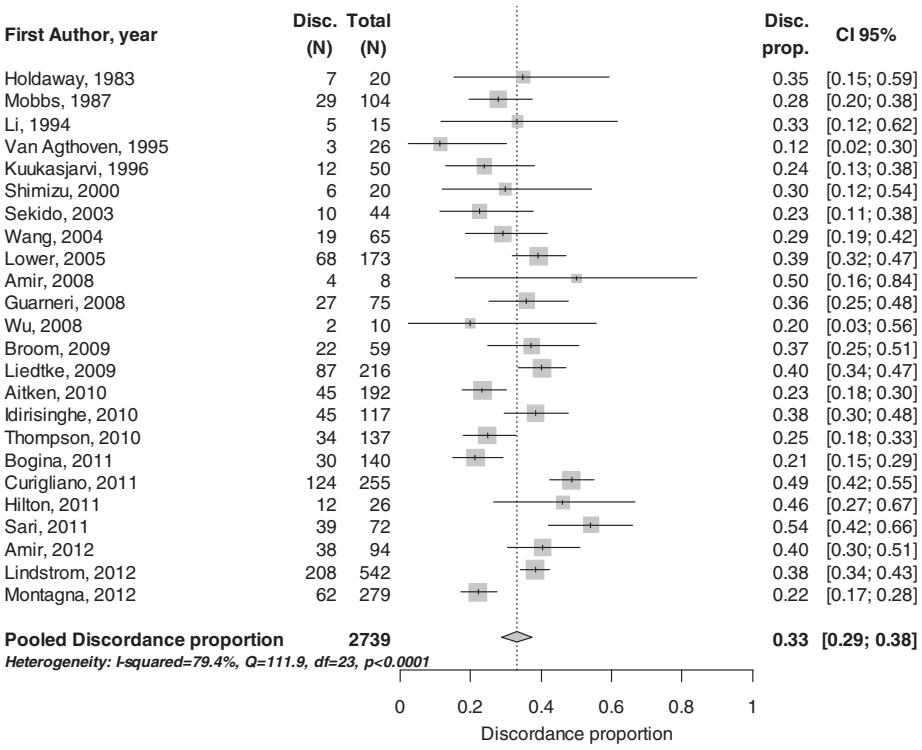


Fig. 4. Forest plot for proportion of discordance progesterone receptor (PgR).

4. Discussion

The assessment of biological changes in metastatic disease and the question whether and why a metastatic deposit should be biopsied is still a debated topic in breast cancer. In this study, we meta-analysed published data on ER, PgR and HER2 status discordance between primary breast cancer and recurrent tumours. Our meta-analysis, that was unaffected by publication bias, showed that the rates of discordance for ER, PgR and HER2 were 20%, 33% and 8%, respectively. Since the earlier studies reporting discordance in ER, PgR and HER2 status between primary tumour and relapses have been published, two alternative explanations arose, pointing to technical issues, such as poor reproducibility of the immunohistochemical technique, or to a true biological manifestation of tumour heterogeneity, a controversy lasting more than 40 years and still unresolved. The lack of a perfect reproducibility in the immunohistochemical or FISH assessment of ER, PgR and HER2 status has been repeatedly reported in prospective trials based on central pathology review [57,58], and a mathematical model has been proposed foreseeing a discordance rate of at least 10% even using an ideal test yielding 95% accuracy, sensitivity and specificity, a scenario reasonably far from the clinical practice, where additional variables including time and type of fixation, sampling issues and misinterpretation of the results may further affect reproducibility [59].

Although clearly established, it is likely that the technical issue alone does not explain thoroughly the variation of ER, PgR and HER2 status between primary tumours and relapses observed in our meta-analysis. If occurring as a consequence of an analytical flaw, one could expect that the discordance rates among the antigens tested would be roughly the same, while actually they were 20%, 33% and 8% for ER, PgR and HER2, respectively. Furthermore, if the discrepancy was merely technical, it seems conceivable that adding to IHC a potentially more objective and reproducible tool like FISH would significantly reduce the discordance rate: on the contrary, the HER2 discordance rate reported in the present analysis was 10% in the studies using IHC and FISH, and 5% in studies using IHC only. Likewise, we found that the prevalence of negative conversion outnumbered that of positive conversion (24% versus 14%, 46% versus 15%, 13% versus 5%, for ER, PgR and HER2, respectively), while they would be very similar if occurring by chance only for technical reasons. Based on more than 4000 patients for ER, and almost 3000 for PgR and HER2, this highly statistically significant finding is in line with the notion that a large fraction of patients originally carrying endocrine-responsive or HER2-positive tumours eventually develop resistance to their specific treatments, possibly as the result of a selective selection fostering ER/PgR and HER2-negative tumour clones in the metastatic sites. Although the loss of PgR immunoreactivity, that was the most frequent change observed in our meta-analysis, does not usually influence clinical decision making, it should be taken into account since it may reflect a shifting to a more aggressive phenotype with a documented reduced

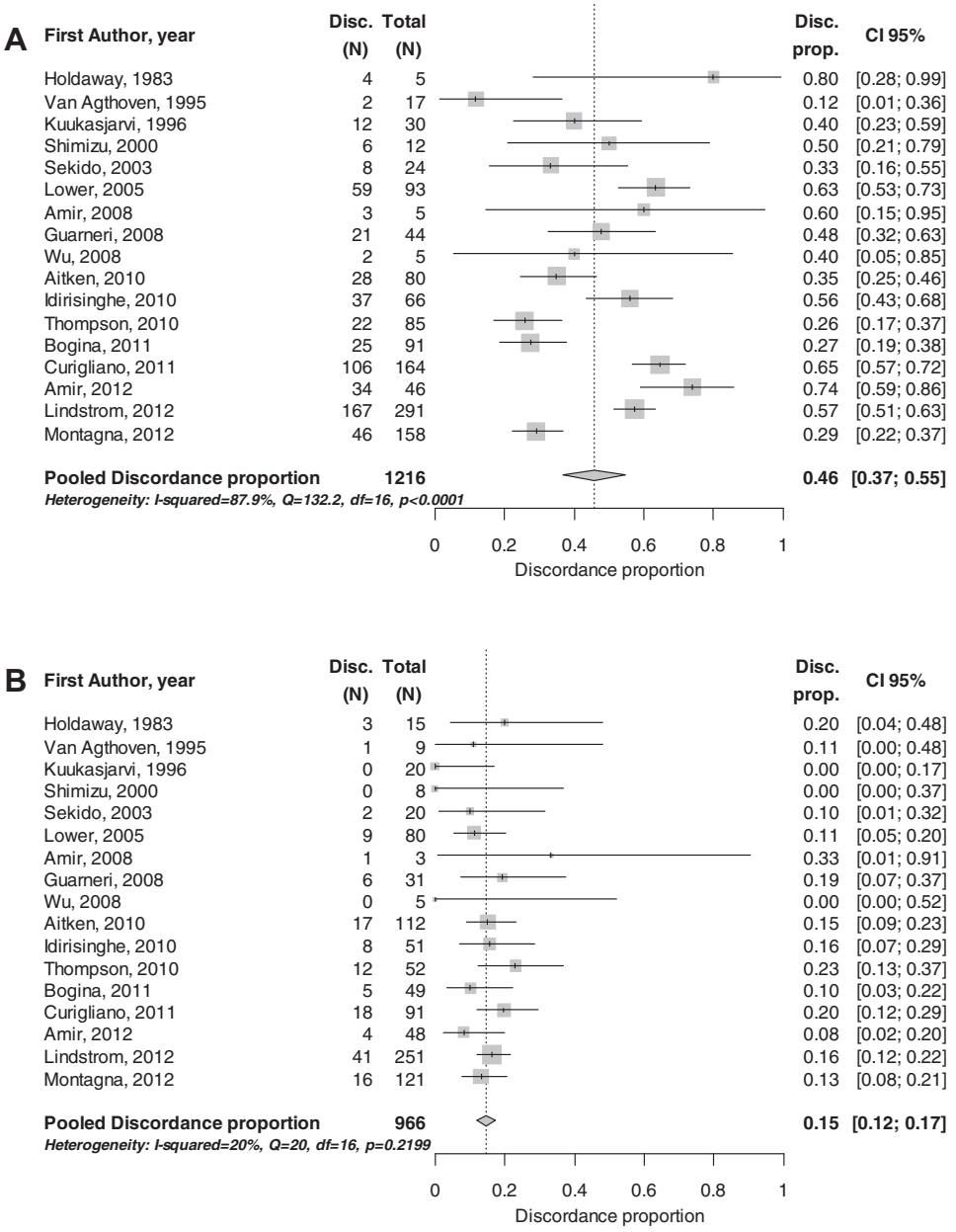


Fig. 5. (A) Forest plot for proportion of negative conversion progesterone receptor (PgR). (B) Forest plot for proportion of positive conversion PgR.

overall survival [60,61]. Finally, the licensing of detailed guidelines for optimising the immunohistochemical analyses, coupled with the availability of detection kits for ER, PgR and HER2, would have lowered the discordance rate in most recent studies, while we reported that the date of diagnosis did not significantly influence the discrepancy in ER, PgR and HER2 status between primary tumour and bone metastases in a retrospective series of breast cancer patients whose primary tumour characteristics were addressed by using different primary antibodies over a 12-year period [62]. Unfortunately, most of the studies included in this meta-analysis did not report details on the date of diagnosis and relapse, thus preventing us from confirming this finding in a larger scale.

On the other hand, recent studies based on next generation sequencing shed new light on tumour heterogeneity, reinforcing the hypothesis that variation in ER, PgR and HER2 status may actually reflect clonal genome evolution. Tumour heterogeneity may be attributable to tumour biological drift, selective pressure of therapy leading to clonal selection with the development of a novel tumour cell clone, or the presence of small sub-clones routinely undetected within the primary tumour. Along this line, as prospectively reported by Hilton and colleagues [45] a significant ER discordance rate between primary

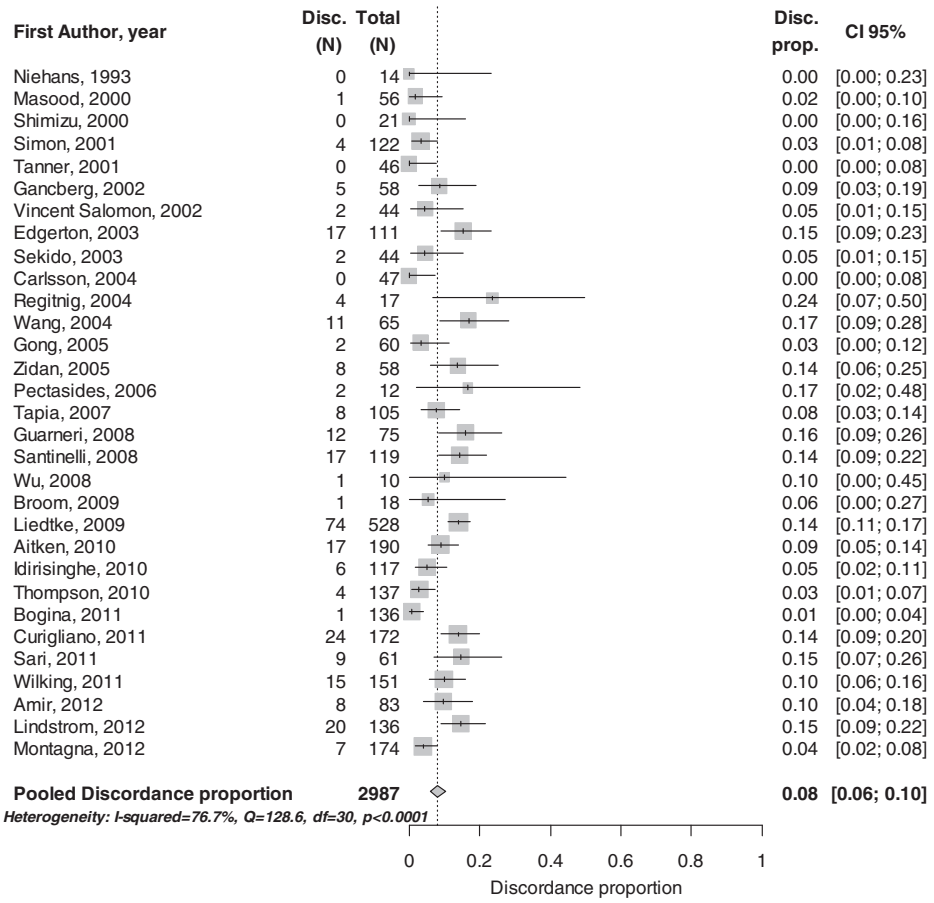


Fig. 6. Forest plot for proportion of discordance human epidermal growth factor receptor 2 (HER2).

tumour and metastatic deposits occurred, and a full concordance among metastases arising in multiple bone sites, suggesting the occurrence of a metastasising clone diverging in terms of ER immunoreactivity from the primary tumour. Whether and how ER, PgR and HER2 conversion modifies the treatment schedule and affects breast cancer patients survival has not been fully elucidated, and the available data are scarce and conflicting, as well as the optimal time to retest tumour biology. In this regard, clinical judgment remains essential to guide a reassessment of tissue biology, for instance whenever the metastasis occurs long after tumour diagnosis, arises during an unusual clinical course with early and frequent treatment failures or may guide the administration of targeted therapies. As for survival outcomes, Amir and colleagues [53] did not find any significant difference in overall survival and time to treatment failure, while as reported by Dieci and colleagues [63] negative conversion of hormone receptors and HER2 was significantly associated to a reduced post-relapse survival and, for HER2 only, overall survival. In the same context, patients with concordant receptor status (at least one receptor positive) have been reported to have a significantly improved post-recurrence [42] or overall survival [64], pointing to a role of hormonal receptor and/or HER2 change in the management of metastatic breast cancer patients [53,56,65]. Along this line, the adding of trastuzumab has been recently reported to improve survival in patients with HER2-positive metastatic deposits which did not receive a previous anti-HER2 therapy [66].

Unfortunately, relevant ethical constraints prevented planning randomised prospective trials, which could overcome these inconsistencies.

Authors' contributions

Study design: Gaetano Aurilio, Davide Disalvatore, Vincenzo Bagnardi, Giuseppe Viale, Franco Nolè.

Literature search: Gaetano Aurilio, Davide Disalvatore, Giancarlo Pruneri.

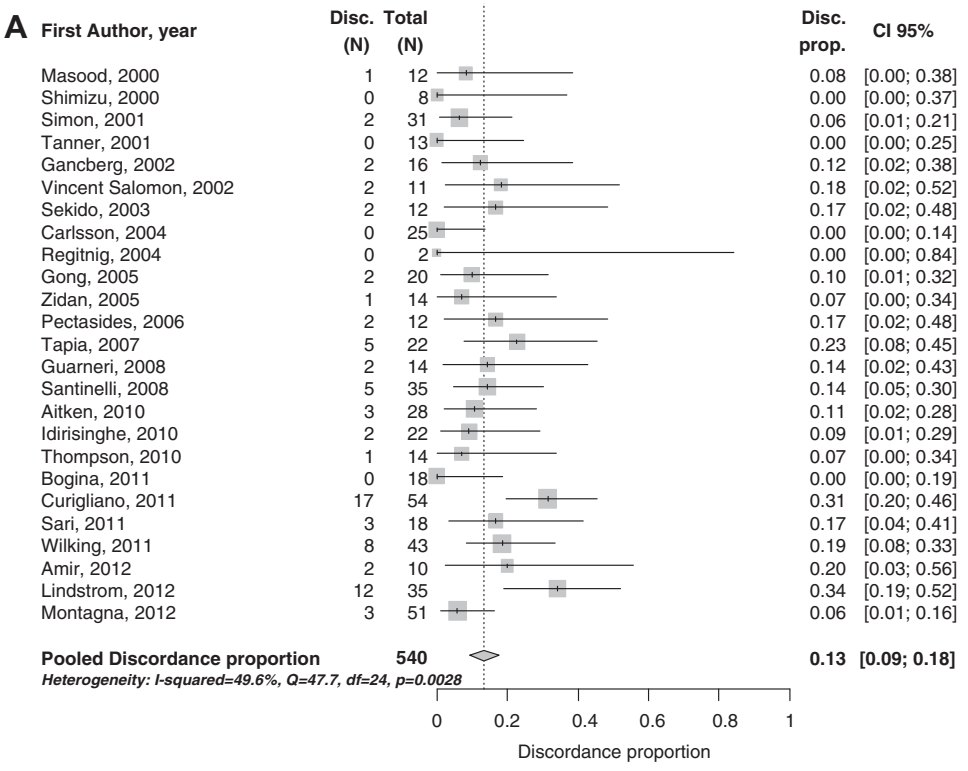
Figures: Davide Disalvatore, Vincenzo Bagnardi.

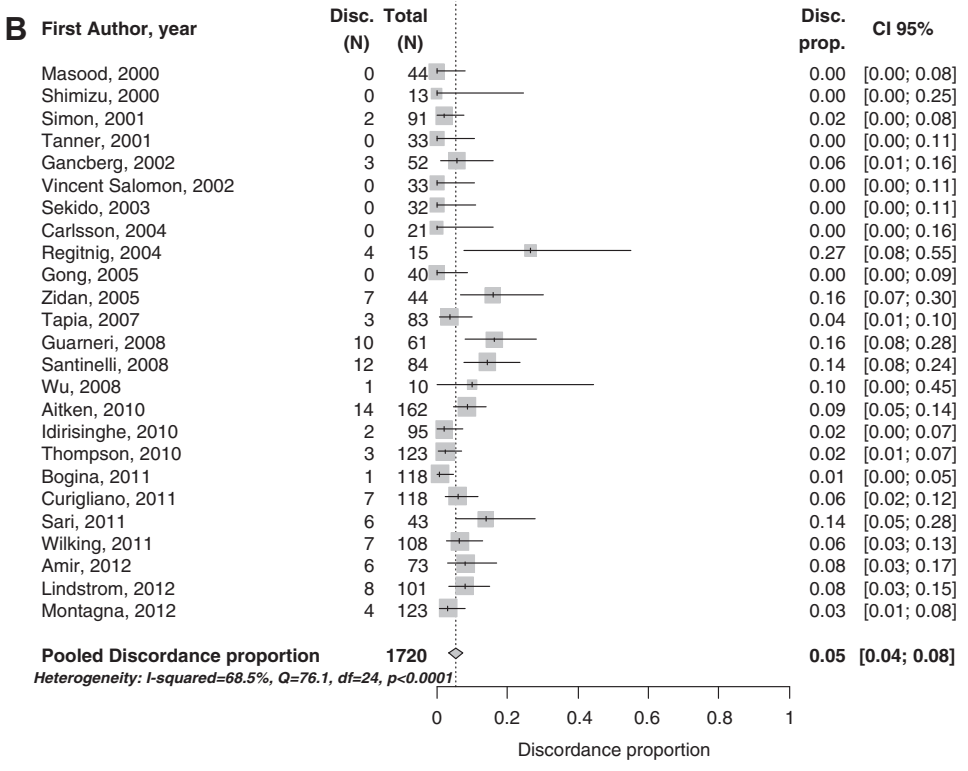
Data collection: Gaetano Aurilio, Davide Disalvatore.

Data analysis: Davide Disalvatore, Vincenzo Bagnardi, Gaetano Aurilio, Giancarlo Pruneri.

Data interpretation and final approval: Gaetano Aurilio, Davide Disalvatore, Vincenzo Bagnardi, Giuseppe Viale, Franco Nolè, Giancarlo Pruneri, Aron Goldhirsch, Giuseppe Curigliano, Fernando De Vita, Elisabetta Munzone, Angela Sciandivasci, Laura Adamoli.

Manuscript writing: Gaetano Aurilio, Giancarlo Pruneri, Davide Disalvatore, Vincenzo Bagnardi.





p-value Between negative conversion and positive conversion= 0.0004

Fig. 7. (A) Forest plot for proportion of negative conversion human epidermal growth factor receptor 2 (HER2). (B) Forest plot for proportion of positive conversion HER2.

Role of the funding source

There is no funding source.

Conflict of interest statement

None declared.

Appendix A

Characteristics of studies included in the meta-analysis.

First author (year)	Country	Design	Site	Oestrogen receptor (ER)	Progesterone receptor (PgR)	Human epidermal growth factor receptor 2 (HER2)	Fluorescent In Situ Hybridisation (FISH) (yes/no)
Holdaway (1983) [9]	New Zealand	R	LR-DM	Yes	Yes	No	–
Mobbs (1987) [10]	Toronto	R	LR-DM	Yes	Yes	No	–
Andersen (1988) [11]	Denmark	R	LR-DM	Yes	No	No	–
Kamby (1989) [12]	Denmark	P	LR-DM	Yes	No	No	–
Spataro (1992) [54]	United States of America (USA), Switzerland, Italy, Sweden	R	LR-DM	Yes	No	No	–
Niehans (1993) [13]	USA	R	LR-DM	No	No	Yes	No
Li (1994) [14]	USA	R	LR-DM	Yes	Yes	No	–
Johnston (1995) [15]	England	R	LR-DM	Yes	No	No	–
Nedergaard (1995) [16]	Denmark	R	LR	Yes	No	No	–
van Agthoven (1995) [17]	Netherlands	R	LR	Yes	Yes	No	–
Kuukasjärvi (1996) [18]	Finland	R	LR-DM	Yes	Yes	No	–
Masood (2000) [19]	USA	R	DM	No	No	Yes	No
Shimizu (2000) [20]	Japan	R	LR-DM	Yes	Yes	Yes	No
Simon (2001) [21]	Switzerland	R	LR	No	No	Yes	Yes
Tanner (2001) [22]	Finland	R	LR-DM	No	No	Yes	Yes
Zheng (2001) [23]	China	R	LR	Yes	No	No	–
Gancberg (2002) [24]	Switzerland	R	DM	No	No	Yes	No
Vincent-Salomon (2002) [25]	France	R	DM	No	No	Yes	No
Edgerton (2003) [26]	USA	R	LR-DM	No	No	Yes	Yes
Iguchi (2003) [27]	Japan	R	LR	Yes	No	No	–
Sekido (2003) [28]	Japan	R	LR-DM	Yes	Yes	Yes	Yes
Carlsson (2004) [29]	Sweden	R	LR	No	No	Yes	Yes
Regitnig (2004) [30]	Austria	R	DM	No	No	Yes	Yes
Wang (2004) [31]	China	R	DM	Yes	Yes	Yes	No
Gong (2005) [32]	USA	R	LR-DM	No	No	Yes	Yes
Lower (2005) [33]	USA	R	LR-DM	Yes	Yes	No	–
Zidan (2005) [34]	Israel	R	LR-DM	No	No	Yes	Yes
Pectasides (2006) [35]	Greece	P	DM	No	No	Yes	Yes
Tapia (2007) [36]	Switzerland	R	DM	No	No	Yes	Yes

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2013.10.004.

Table (*continued*)

First author (year)	Country	Design	Site	Oestrogen receptor (ER)	Progesterone receptor (PgR)	Human epidermal growth factor receptor 2 (HER2)	Fluorescent In Situ Hybridisation (FISH) (yes/no)
Gomez-Fernandez (2008) [37]	USA	R	LR-DM	Yes	No	No	–
Guarneri (2008) [38]	Italy	R	LR-DM	Yes	Yes	Yes	Yes
Santinelli (2008) [39]	Italy	P	LR-DM	No	No	Yes	Yes
Wu (2008) [40]	USA	R	DM	Yes	Yes	Yes	Yes
Amir (2008) [44]	Canada	P	DM	Yes	Yes	No	–
Broom (2009) [41]	Canada	R	DM	Yes	Yes	Yes	Yes
Liedtke (2009) [42]	USA	R	LR-DM	Yes	Yes	Yes	Yes
Idirisinghe (2010) [46]	Singapore	R	LR-DM	Yes	Yes	Yes	No
Thompson (2010) [48]	England	P	LR-DM	Yes	Yes	Yes	Yes
Aitken (2010) [43]	England	R	LR	Yes	Yes	Yes	Yes
Sari (2011) [47]	Turkey	R	LR-DM	Yes	Yes	Yes	Yes
Hilton (2011) [45]	Canada	P	DM	Yes	Yes	No	–
Bogina (2011) [49]	Italy	R	LR-DM	Yes	Yes	Yes	No
Curigliano (2011) [50]	Italy	R	DM	Yes	Yes	Yes	Yes
Gong (2011) [51]	USA	R	LR-DM	Yes	No	No	–
Wilking (2011) [52]	Sweden	R	LR-DM	No	No	Yes	Yes
Amir (2012) [53]	Canada	P	DM	Yes	Yes	Yes	Yes
Montagna (2012) [55]	Italy	R	LR	Yes	Yes	Yes	No
Lindström (2012) [56]	Sweden	R	LR-DM	Yes	Yes	Yes	Yes

LR: loco-regional; DM: distant metastases; P: prospective; R: retrospective.

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