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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.