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HER2 assessment in a large Kaiser Permanente case-control study: Comparison of fluorescence in situ hybridization (FISH) and quantitative reverse transcription polymerase chain reaction (RT-PCR) performed by central laboratories

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Background

The optimal method to assess HER2 status remains highly controversial. ASCO/CAP guidelines mandate laboratories to demonstrate $\geq 95\%$ concordance to another laboratory or methodology before reporting clinical patient HER2 results. Here we compare central laboratory HER2 assessed by FISH and quantitative RT-PCR using Oncotype DX in patients from a large Kaiser Permanente case-control study.

Methods

Breast cancer specimens from the Kaiser Oncotype DX study (Habel et al, Breast Can Res 2006) were examined. For HER2 measurement by FISH, analysis for amplification ratio was conducted by a central laboratory (Yaziji et al, JAMA 2004) with positive > 2.2 , equivocal 1.8 to 2.2, and negative < 1.8 . Quantitative RT-PCR analysis for HER2 used Oncotype DX and pre-defined cutoffs: positive ≥ 11.5 units, equivocal $\geq 10.7 - < 11.5$ units, and negative < 10.7 units (each unit represents a 2-fold change in expression). Concordance analyses were conducted according to ASCO/CAP guidelines (Wolff et al, 2006). Conditional logistic regression was used to estimate the association between HER2 by RT-PCR and risk of breast cancer death, according to a prespecified analysis plan.

Results

12% (67/568) of patients were HER2+ by RT-PCR. 11% (60/568) of patients were HER2+ by FISH. 55 of the 60 patients who were HER2+ by FISH were HER2+ by RT-PCR. 55 of the 67 patients who were HER2+ by RT-PCR were HER2+ by FISH. Of the 12 patients who were HER2+ by RT-PCR but not by FISH, 11 were HER2- and one was FISH HER2 equivocal. The concordance for positive and negative HER2 cases by central FISH and central RT-PCR was 97% (95% CI: 96%, 99%). There was a significantly greater risk of breast cancer death in patients with HER2 ≥ 11.5 (OR=1.8, 95% CI 1.1, 3.0) compared to patients with HER2 ≤ 10.7 , but not in patients with HER2 $> 10.7 - < 11.5$ (OR=0.7, 95%CI 0.4, 1.2) compared to patients with HER2 ≤ 10.7 . There were 71 (12.5%) polysomy cases.

Conclusion: There is a high degree of concordance between RT-PCR using Oncotype DX and central laboratory FISH assessment of HER2 status.

HER 2	Central FISH +	Central FISH equivocal	Central FISH -	Total RT-PCR
RT-PCR +	55	1	11	67
RT-PCR equivocal	4	5	79	88
RT-PCR -	1	4	408	413
Total FISH	60	10	498	568