

## **The upgraded role of HER3 and HER4 receptors in breast cancer.**

[Koutras AK](#), [Fountzilias G](#), [Kalogeras KT](#), [Starakis I](#), [Iconomou G](#), [Kalofonos HP](#).

### **Source**

Department of Medicine, University Hospital of Patras, Rion, Greece. [angkoutr@otenet.gr](mailto:angkoutr@otenet.gr)

### **Abstract**

The human epidermal growth factor receptor (HER) family comprises four homologous members. The activation of these receptors affects essential tumorigenic processes and plays a crucial role in the pathogenesis of breast cancer. Among HER family members, EGFR and HER2 are the most studied. However, accumulating data provide evidence for the significance of HER3 and HER4 alterations in breast carcinogenesis. The combination of HER2 and HER3 receptors may be critical in breast cancer growth and progression. Moreover, HER3 may provide a route for resistance to agents targeting EGFR or HER2. Although a number of studies have demonstrated that HER3 overexpression is associated with poor prognosis in patients with breast cancer, other studies have indicated that HER3 overexpression may be a positive prognostic factor. With respect to HER4 receptor, the existing evidence suggests that HER4 signalling promotes differentiation and growth inhibition of breast cancer cells. In addition, HER4 is more consistently related with a favourable prognosis in breast cancer. HER4 has multiple different activities in the breast, and many of these functions are mediated by a soluble HER4 intracellular domain. In addition, loss of HER4 expression may represent a marker for resistance to tamoxifen. Because of the functional interdependency among the HER receptors, it is possible that the effect on cell proliferation and tumor growth depends on receptor trans-signalling. Therefore, clarifying how and the extent to which these different signalling pathways interact in breast carcinogenesis, may lead to additional therapeutic opportunities. This review presents an update on the role of HER3 and HER4 receptors in breast cancer. Moreover, we provide current data relating to the prognostic significance of these receptors, as well as their impact on the activity of HER-targeting therapies in patients with breast cancer.