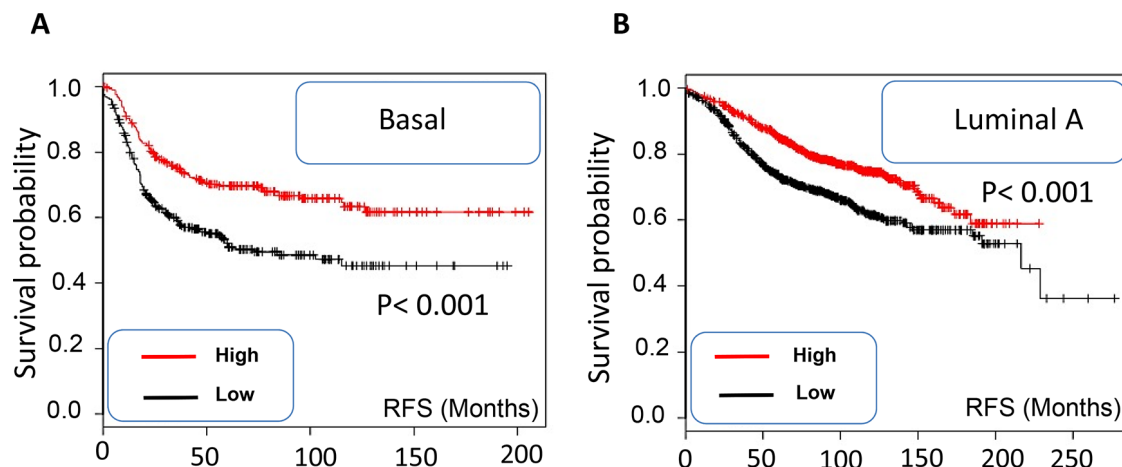


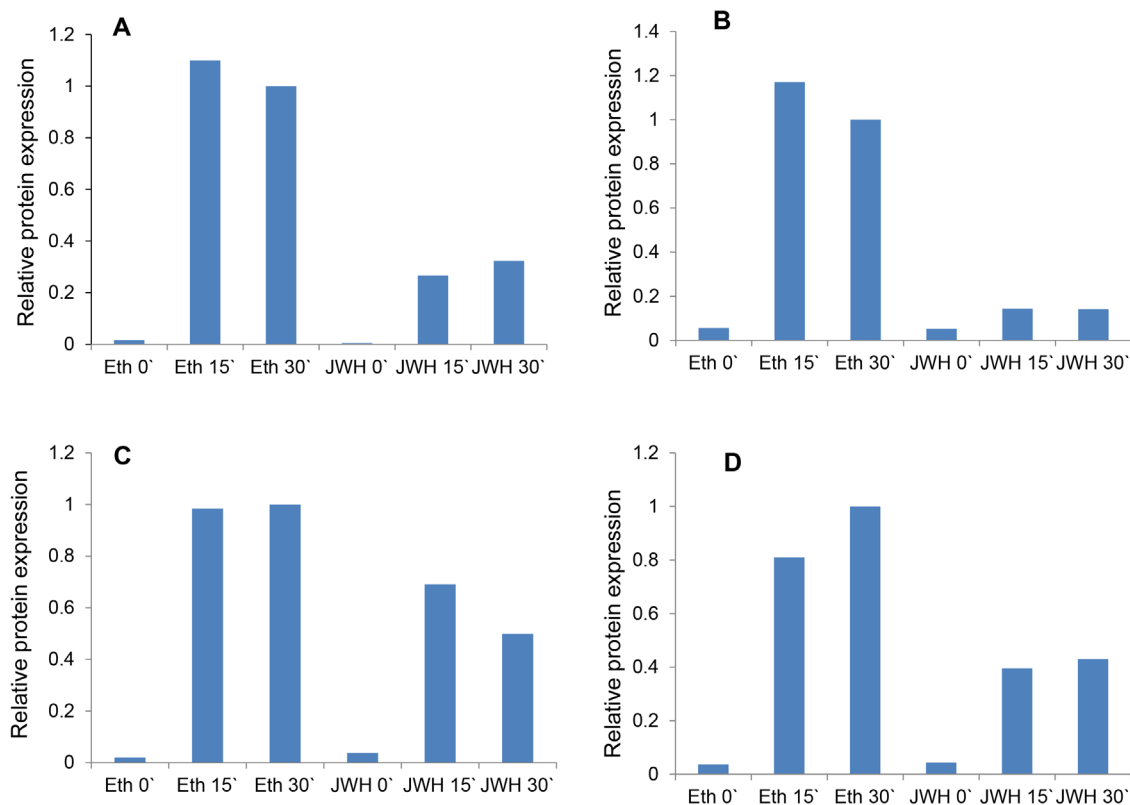
Novel role of cannabinoid receptor 2 in inhibiting EGF/EGFR and IGF-I/IGF-IR pathways in breast cancer

SUPPLEMENTARY FIGURES

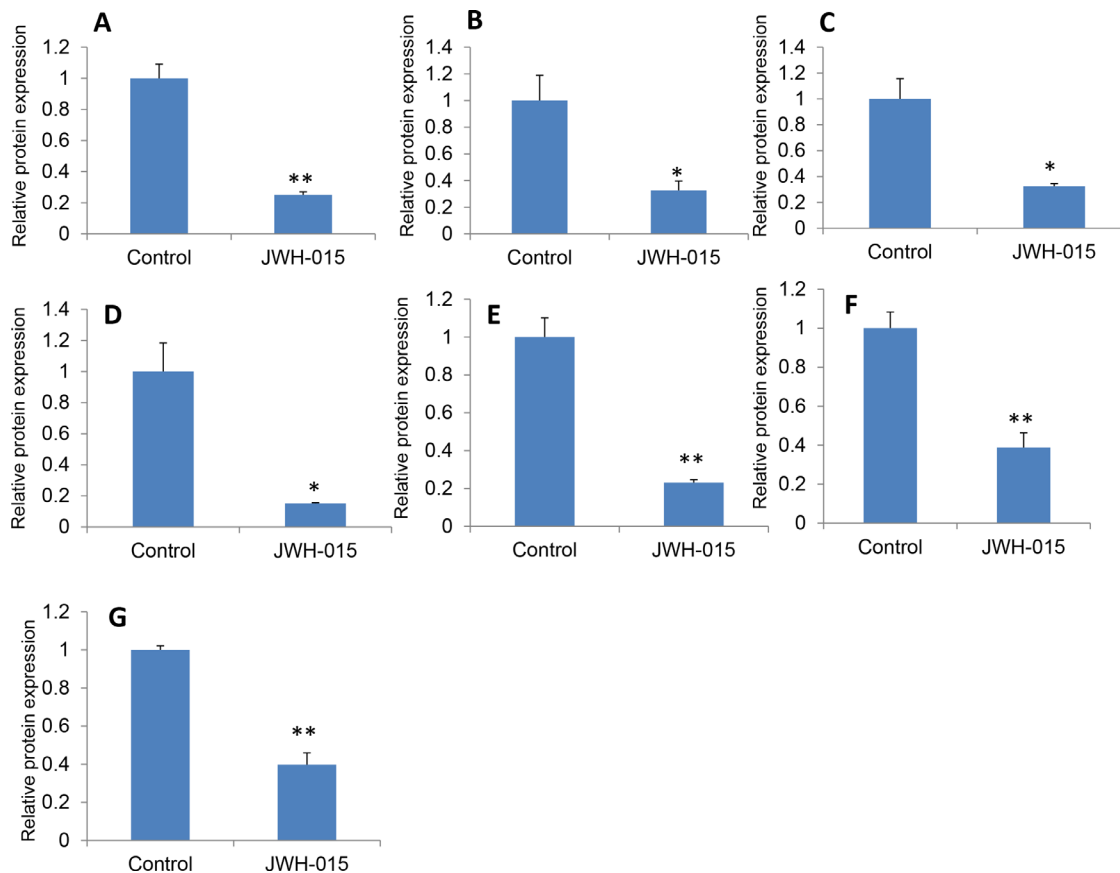


Supplementary Figure S1: Correlation of CNR2 to breast cancer patients' prognosis of Basal and luminal A subtypes.

A. Kaplan Meier blot showing recurrence free survival (RFS) of high/low expressing CNR2 breast cancer patients of Basal subtype. P value = $\sim$ zero. **B.** Kaplan Meier blot showing recurrence free survival (RFS) of high/low expressing CNR2 breast cancer patients of luminal A subtype. P value = $1e^{-05}$.

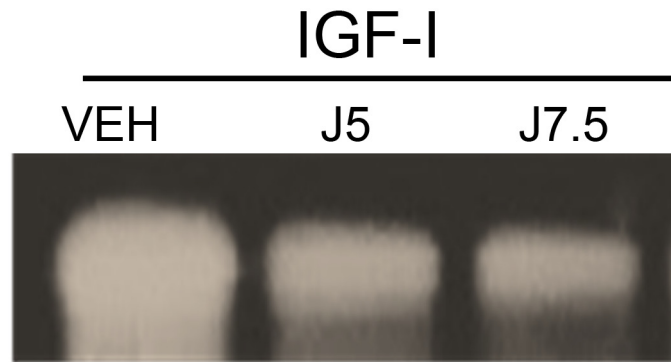


Supplementary Figure S2: Quantification of protein expression showing that JWH-015 inhibits IGF-I induced activation of IGF-IR and AKT. SUM159 cells were treated with JWH-015 and stimulated with IGF-I (50 ng/ml) for 0, 15 or 30 minutes then the cell lysates were used for western blot analysis for the indicated proteins and relative p-IGF-IR/IGF-IR **A**, and relative p-AKT/AKT expressions **B**, have been quantified for every condition. MCF-7 cells were treated with JWH-015 and stimulated with IGF-I (50 ng/ml) for 0, 15 or 30 minutes then the cell lysates were used for western blot analysis for the indicated proteins and relative p-IGF-IR/IGF-IR **C**, and relative p-AKT/AKT **D**, expressions have been quantified for every condition.

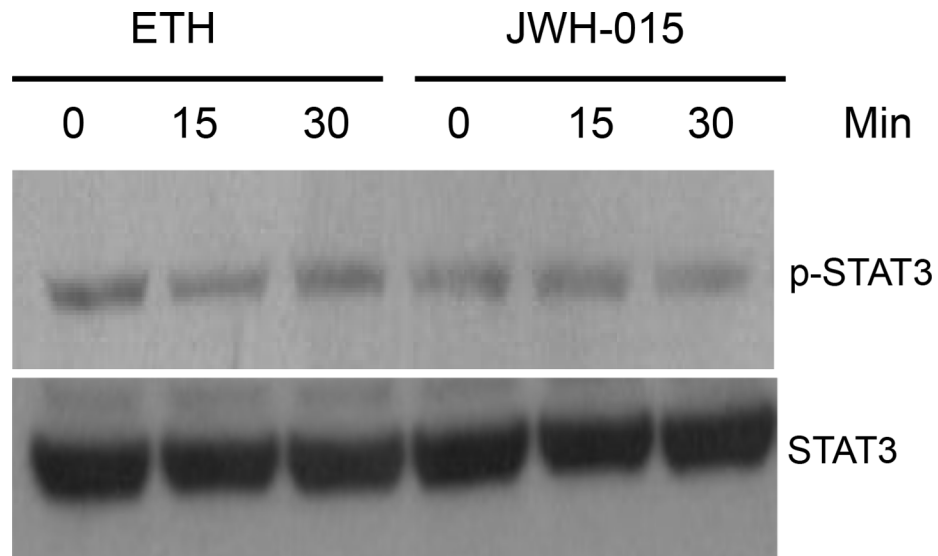


Supplementary Figure S3: Quantification of protein expression in the vehicle and JWH-015-treated tumor lysates.

Nude mice were orthotopically injected with SUM159 cells and treated with vehicle or JWH-015 for 4 weeks and the tumors were harvested for western blot protein analysis. Protein expression has been quantified by image-j software for every condition as a relative expression of phosphorylated protein to total protein expression as follows **A.** p-EGFR/EGFR, **B.** p-IGF-IR/IGF-IR, **C.** p-STAT3/STAT3, **D.** p-AKT/AKT and **E.** p-ERK/ERK. Nude mice were orthotopically injected with MCF-7 cells and treated with vehicle or JWH-015 for 4 weeks and the tumors were harvested for western blot protein analysis. Protein expression has been quantified by image-j software for every condition as a relative expression of phosphorylated protein to total protein expression as follows **F.** p-IGF-IR/IGF-IR and **G.** p-AKT/AKT.



Supplementary Figure S4: JWH-015 inhibits MMP-2 secretion in SUM159 cells. SUM159 cells were treated with vehicle or JWH-015 5 or 7.5 μ M in presence of IGF-I and the collected conditioned media were subjected to gelatin zymography to detect MMP-2.



Supplementary Figure S5: JWH-015 does not affect STAT3 activation. SUM159 cells were treated with vehicle or JWH-015 for 24h, then stimulated with IGF-I (50 ng/ml) for 0,15 and 30 minutes and the cells were lysed for detection of the indicated protein by western blot.