ABSTRACT

Introduction: Androgen receptor (AR) is a member of the steroid nuclear receptor family, which includes estrogen receptor (ER) and progesterone receptor (PR). In breast cancer, AR is expressed in 50–80% of tumors, cross-talks with ER in luminal subtype and is related to the resistance to hormonal therapies. High AR to ER ratio was reported to associate with a favorable prognosis. Multiple publications reported that high AR expression was associated with better survival in breast cancer; however, how they determined the level of expression were somewhat arbitrarily. In fact, there is a criticism in the field that the data are incompatible between the studies due to lack of standardized staining method of AR. Indeed, some reported that high AR expressed tumors showed significantly shorter survival. Given this controversy we investigated the association of AR expression and patient survival using gene expression data of the publically available large cohort.

Methods: Clinical and RNA-sequence data were obtained from The Cancer Genome Atlas (TCGA) through cBioportal. High or low expression of AR was determined by automated scanning and selecting the threshold yielding the lowest p-value of overall survival (OS).

Utilizing same cutoff point, survival analysis and Gene set enrichment analysis (GSEA) were conducted between AR high and low expression group in subgroup based on ER status.

Results: Among 1093 TCGA breast cancer cohort, there were 805 ER positive patients (73.7%) and 237 ER negative patient (21.7%). AR expression were significantly higher in ER positive tumors compare to ER negative tumors (0.16 ± 0.08 vs. 0.58 ± 0.39, p < 0.001). The largest difference in OS between AR expression high vs low was achieved at the cutoff point of 820 and 270 patients; however, the difference was not significant in whole cohort (5-year OS rates: 84.2% vs. 80%, p = 0.085). On the other hand, AR high expression group showed significantly worse OS in ER positive patients (5-year OS rates: 84.2% vs 80%, p = 0.007), whereas there was no significant difference in ER negative patients (5-year OS rates: 74.8% vs 76.5%, p = 0.572). To explore the underlying mechanism of worse survival in AR high expressed tumor in ER positive patients, GSEA was conducted between AR high and low expression group in ER positive patients. GSEA demonstrated that high expression of AR tumors enriched gene set that down-regulated in response to ultraviolet (UV) radiation (NES=1.97, p<0.001) and low AR expressed tumors enriched gene set that up-regulated in response to UV radiation (NES=1.50, p=0.027). Our result may imply that ER positive breast cancer with AR high expression tumors have worse OS because they respond less to radiation therapy. GSEA demonstrated that high expression of AR tumors enriched gene set that down-regulated in response to ultraviolet (UV) radiation, protein secretion and early estrogen response. On the other hand, low expression of AR tumors enriched gene set related to DNA repair.

Conclusion: When the cut-point determined to lower quartile in whole cohort, according our analysis, high expression of AR showed worse OS in ER positive tumors. The mechanical of these results may be related the estrogen response and the DNA repair.

There is no difference in prognosis in TCGA cohort.

AR mRNA expression is highest in ER positive and HER2 subtype in TCGA cohort.

There is no difference in prognosis but approached significance in Luminal A cohort in TCGA.

High Androgen Receptor expression tumors have worse overall survival in ER positive breast cancer

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Disclosure

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