CLINICAL SIGNIFICANCE OF ESTROGEN RECEPTOR 1 GENE PROMOTOR METHYLATION IN HORMONAL THERAPY RESISTANT BREAST CANCER PATIENTS

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Introduction

Breast cancer (BC) remains the most common malignancy in women worldwide, and is the leading cause of female cancer-related mortality. This warrants early diagnosis and the improvement of specific subtype treatments, thus leading to significant improvements of the 5-year survival rates. However metastatic breast cancer (MBC) still remains incurable.

About 70% of breast cancer patients express estrogen receptor alpha (ERα) and are considered estrogen dependent. Thus these hormone receptor positive patients are candidates for endocrinal therapy.

Unfortunately, the efficacy of endocrine therapy is limited by the development of BC endocrine resistance which is considered a major challenge in both the adjuvant and metastatic settings, and nearly half of ER+ve BC patients treated with hormonal therapy become unresponsive to treatment over time. This warrants the need for investigating markers that reflect hormonal resistance mechanisms, such as epigenetic alterations including aberrant DNA methylation and chromatin remodeling.

An epigenetic marker like the ESR1 promoter methylation might eventually be a one promising tool that help clinicians make the right decisions, since ESR1 gene promotor methylation might potentially affect the response to endocrine treatment.

Aim of the work

The aim of the present study was to evaluate the methylation status of ESR1 gene promoter in ER+ primary breast cancer and its corresponding metastases, in order to correlate the methylation status with the development of resistance to endocrine therapy and clinical outcome in ER+ BC.

Patients and Methods

Patients

From the Clinical Oncology and Nuclear Medicine Department at Alexandria Main University Hospital and Medical Research Institute, 50 patients with recurrent and/or metastatic breast cancer were identified and included in our study. These 50 MBC patients were known to be treated for their primary tumors using hormonal treatment and their tissue samples (1ry and 2ry) were available at the time of collection.

Methods

Tissue tumor biopsies and/or formalin fixed paraffin embedded tissue (FFPE) (confirmed by histopathological examination) of the breast cancer primary tumor and its corresponding recurrence/metastasis were used in serial sections to finally detect the methylation status of the promoter region of the ESR1 gene through a series of steps; first extraction of DNA from 1ry and 2ry tissue samples, second the bisulphite conversion of the extracted DNA that cause the conversion of unmethylated cytosine into uracil, but it has no effect on methylated cytosine which remain unchanged. Finally, real-time methylation specific PCR was used for the detection of methylation status of the promoter of ESR1 gene

Results

Among the studied patients; the methylation status of the ESR1 gene promoter was assessed within the primary and secondary tumors. Within the primary tumors, 48 (96.0%) were unmethylated, while 2 (4.0%) were Methylated/Hemi-methylated. Within the secondary tumors, 35 (70.0%) were unmethylated, 15 (30.0%) were Methylated/Hemi-methylated. A statistically significant difference was detected between the primary and secondary tumor as regards to the methylation status (p= 0.001)

Table: Distribution of the studied cases according to tumor methylation status (n = 50)

	Primary tumor		Secondary tumor		McNp
	No.	%	No.	%	
Methylation status					
Un-methylated	48	96.0	35	70.0	0.001*
Methylated/ hemi methylated	2	4.0	15	30.0	

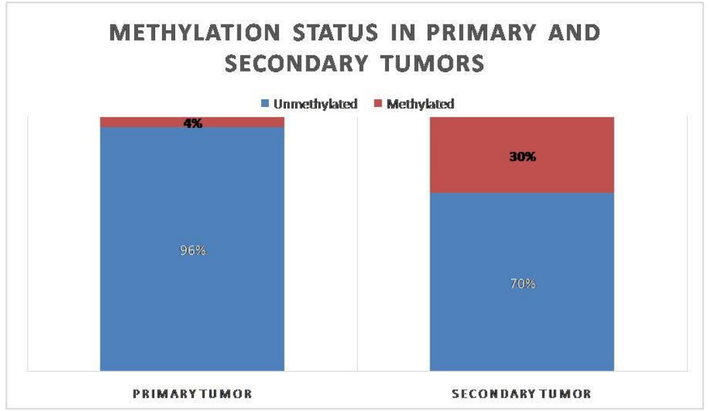

Figure: Distribution of the studied cases according to tumor methylation status (n=50)

Conclusion

- There was a significant increase in the methylation of ESR1 gene promoters in secondary breast cancer in comparison to their previous primary tumors in ER positive breast cancer patients who had undergone hormonal treatment.
- Assessment of methylation status of the promoter of ESR1 in patients with BC may be considered as a new indicator that can aid in the assessment of resistance to hormonal treatment and monitoring of disease progression.